

**WHO Vision for Medicines Safety
No country left behind:
worldwide pharmacovigilance
for safer medicines, safer patients**

The aim of the Newsletter is to disseminate regulatory information on the safety 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:

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*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 around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

This newsletter includes a summary of discussions and key recommendations from the 15th meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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Adrenaline interaction with antipsychotics

Hypotension: Contraindication revised

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have requested that precautions for adrenaline and antipsychotics (e.g. aripiprazole, Abilify®) preparations should be revised to specify that co-administration is not contraindicated if adrenaline is used for emergency treatment of anaphylaxis.

Adrenaline is the first-line drug used for treatment of anaphylaxis in Japan. Antipsychotic agents and adrenaline co-administration was previously contraindicated due to an interaction causing adrenaline reversal and hypotension.

The Japanese Society of Allergology requested to remove this contraindication. The PMDA investigated the safety of co-administration of adrenaline preparations used for the emergency treatment of anaphylaxis in patients who are on antipsychotic agents with α -blocking actions. The PMDA concluded that anaphylaxis is a fatal condition that requires prompt emergency treatment. Therefore use of adrenaline preparations for anaphylaxis is considered to be acceptable even though there is a risk of decreased blood pressure induced by adrenaline reversal.

Reference:

Revision of Precautions, MHLW/PMDA, 27 March 2018 (www.pmda.go.jp/english/)

Amlodipine

1. Risk of Alopecia

India. The National Coordination Centre - Pharmacovigilance Programme

of India (NCC-PvPI), Indian Pharmacopoeia Commission (IPC) has made a recommendation to the Central Drugs Standard Control Organisation (CDSCO) requesting that the drug safety label for amlodipine is revised to include alopecia as an adverse drug reaction.

Amlodipine is used for the treatment of angina, hypertension and coronary artery disease. Between July 2011 and August 2017, NCC-PvPI received seven individual case safety reports (ICSRs) of alopecia with amlodipine use. The cases were reviewed by Signal Review Panel (SRP)-PvPI, IPC and they showed a strong causal relationship between amlodipine and alopecia.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

2. Risk of Gingival Hypertrophy

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for amlodipine is revised to include gingival hypertrophy as an adverse drug reaction.

Between July 2011 and March 2018, NCC-PvPI received 44 ICSRs reporting gingival hypertrophy with amlodipine use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC and they suggested a strong causal relationship between amlodipine and gingival hypertrophy.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

Antimalarial drugs

Risk of Stevens Johnson syndrome (SJS)

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for the artesunate combination antimalarial drug (artemether and lumefantrine) is revised to include the risk of Stevens Johnson syndrome.

Artemether-lumefantrine are used in combination for the treatment of uncomplicated malaria. Between July 2011 and March 2018, NCC-PvPI received four ICSRs of SJS with artemether and lumefantrine use. The cases were reviewed by SRP-PvPI, IPC, and a strong causal relationship between artemether, lumefantrine and SJS was suggested.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

Antimicrobials

Precautions against inappropriate use to prevent resistance

Japan. MHLW and PMDA have announced that the product information for antimicrobials will be revised to include instructions for prescribers to consult the Guidance for Appropriate Use of Antimicrobials to decide if administration of an antimicrobial is appropriate for the case they are treating.

The Guidance for Appropriate Use of Antimicrobials was developed in accordance with the National Action Plan on Antimicrobial Resistance 2016-2020 in Japan. The content of the guidance focuses on patients with acute respiratory tract infections and patients with acute diarrhoea.

PMDA examined current package inserts of antimicrobials, and concluded

that it is necessary to update the precautions concerning indications to urge prescribers to refer to the guidance to promote appropriate use.

Reference:

Revision of Precautions, MHLW/PMDA, 27 March 2018 (www.pmda.go.jp/english/)

Atypical antipsychotic

Potential risk of DRESS

Canada. Health Canada has announced that the product safety information for atypical antipsychotics will be updated to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Atypical antipsychotics are indicated to treat mental disorders including schizophrenia, bipolar disorder, and depression.

Health Canada reviewed safety information for all atypical antipsychotics following voluntary updates by the manufacturers for olanzapine (Zyprexa®) and ziprasidone (Zeldox®) to include the risk of DRESS in the product safety information.

Among 43 international reports of DRESS with the use of atypical antipsychotics, 11 reports met the definition of DRESS, and two reports showed a likely link between DRESS and the reported atypical antipsychotic.

Health Canada's review concluded that there may be a link between the risk of DRESS and the use of six other atypical antipsychotics including clozapine, quetiapine, risperidone, aripiprazole, paliperidone, and lurasidone.

Reference:

Summary Safety Review, Health Canada, 10 April 2018 (www.hc-sc.gc.ca)

Carbamazepine

Risk of DRESS

India. NCC-PvPI, IPC has made a recommendation to the CDSCO about the revision of the drug safety label for carbamazepine to include DRESS.

Carbamazepine is used for the treatment of partial seizures with or without secondary generalisation; trigeminal neuralgia; and bipolar disorder. Between July 2011 and March 2018, NCC-PvPI received 33 ICSRs of DRESS syndrome associated with carbamazepine use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC who found a strong causal relationship between carbamazepine and DRESS syndrome.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

(See WHO Pharmaceuticals Newsletters No.1, 2017: HLA-B 1502 genotyping to minimize carbamazepine-induced severe cutaneous adverse reactions in Singapore; No.2, 2016: Risk of Stevens Johnson's Syndrome in India; No.1, 2013: Potential risk of serious skin reactions associated with the HLA-A 3101 allele in UK)

Carvedilol

Risk of hyperkalaemia

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for carvedilol is revised to include hyperkalaemia.

Carvedilol is used for the treatment of hypertension, mild to severe congestive heart failure (CHF), and left ventricular dysfunction (LVD). Between July 2011 and August 2017, NCC-PvPI received four ICSRs reporting hyperkalaemia with carvedilol use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC which suggested a strong causal relationship between carvedilol and hyperkalaemia

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

Cefixime

Risk of mouth ulceration

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the of drug safety label for cefixime is revised to include the risk of mouth ulceration.

Cefixime is used for the treatment of otitis media, respiratory tract infections, and uncomplicated UTIs. Between July 2011 and March 2018, NCC-PvPI received 17 ICSRs reporting mouth ulcerations with cefixime use. A review of the cases by Signal Review Panel (SRP)-PvPI, IPC suggested a strong causal relationship between cefixime and mouth ulceration.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

Dabigatran

Potential risk of liver injury

Canada. Health Canada will be working with the manufacturer of dabigatran (Pradaxa®), to update the safety information to include the potential risk of severe liver injury.

Dabigatran is a blood thinner and is used to prevent certain blood clots from forming or reoccurring (e.g. in the veins of legs), and to treat blood clots in the veins and/or lungs.

Health Canada has reviewed the potential risk of liver injury with dabigatran. At the time of the review Health Canada received 27 Canadian reports and 105 international reports of severe liver injury using dabigatran. Of these reports, 4/ 27 Canadian and 16/105 international reports were assessed. A possible link

between liver injury and the use of dabigatran was shown in 3/4 and 13/16 of these reports respectively.

A review of the scientific literature did not find any published studies that showed increased risk of liver injury in patients treated with dabigatran.

Health Canada's review found that there may be a link between dabigatran and liver injury.

Reference:

Summary Safety Review, Health Canada, 7 May 2018 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.5, 2017: Risk of acute hepatic failure, hepatic function disorder, and jaundice in Japan)

Diclofenac

Risk of Nicolau syndrome

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for diclofenac is revised to include the risk of Nicolau syndrome.

Diclofenac is used for the treatment of acute musculoskeletal pain; arthritis; gout; spondylitis; migraine; and post-operative pain. Between July 2011 and March 2018, NCC-PvPI received six ICSRs of Nicolau syndrome with diclofenac use. A review of the cases by the Signal Review Panel (SRP)-PvPI, IPC suggested a strong causal relationship between diclofenac and Nicolau syndrome.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

Eperisone

Anaphylactic reaction

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has announced that the package insert for

eperisone has been updated to include anaphylactic reaction as an adverse reaction.

Eperisone is a centrally acting skeletal muscle relaxant, used for treatment of muscle spasm accompanied by pain and spastic paralysis caused by nervous system disease.

This recommendation announced by the MFDS was based on expert advice following the evaluation of a signal for reports with serious adverse events by the Korea Institute of Drug Safety and Risk Management (KIDS). At the time of the review, KIDS identified three cases of anaphylactic reactions in patients treated with eperisone. A causal relationship could not be excluded in any of these cases.

Reference:

Based on the communication from MFDS and KIDS, Republic of Korea, March 2018

Gadolinium based contrast agents (GBCAs)

Potential neurological adverse effects

Canada. Health Canada is working with manufacturers to make additional changes to the product information for gadolinium based contrast agents (GBCAs). The changes state that macrocyclic GBCAs are preferable to linear GBCAs in patients who may need repeated GBCA doses, as well as in children and pregnant women.

GBCAs are used to view certain body tissues on magnetic resonance imaging (MRI) scans. There are two structurally distinct categories of commercially available GBCAs in Canada: linear and macrocyclic. Both types are marketed in Canada.

Health Canada carried out a second review of the risk of gadolinium build-up in the

brain and the unknown potential neurological adverse effects. Evidence from published and unpublished studies together with seven international case reports of build-up in the brain linked to the use of GBCAs suggests that risk of gadolinium build-up in the brain is higher with repeated use of GBCAs and with linear GBCAs. This risk was considered to be potentially greater in children, pregnant women, and in people receiving multiple doses of GBCAs. At the time of the review, no neurological adverse effects were linked to gadolinium build-up in the brain.

Reference:

Summary Safety Review, Health Canada, 1 May 2018 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.2, 2018: Omniscan® and intravenous iv Magnevist® no longer authorised; and restrictions of use for other linear agents in UK; No1. 2018: Gadolinium retention in body in Japan and USA; No. 5, 2017: Retention of gadolinium in the brain in New Zealand; No.4, 2017: Restrictions on use in EU, No harmful effects identified with brain retention in USA; No.5, 2015: Possible risk of brain deposits with repeated use in USA)

Isoniazid

Potential risk of pancreatitis

Canada. Health Canada is working with manufacturers to update the safety information for all isoniazid containing products to include the potential risk of pancreatitis.

Isoniazid is indicated to treat tuberculosis.

Health Canada reviewed the potential risk of pancreatitis with the use of isoniazid following an update to the product safety information in the United States.

Health Canada reviewed three Canadian reports, 14 international reports, and published reports and journals in the scientific literature. Health Canada concluded that there is a rare but potential

risk of pancreatitis with the use of isoniazid.

Reference:

Summary Safety Review, Health Canada, 10 May 2018 (www.hc-sc.gc.ca)

Lamivudine

Risk of hearing loss

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for lamivudine is revised to include hearing loss as an adverse reaction.

Lamivudine is used for the treatment of HIV infection in combination of at least two other antiretroviral drugs. Between July 2011 and March 2018, NCC-PvPI received eight ICSRs that reported hearing loss with lamivudine use. A review of cases by the Signal Review Panel (SRP)-PvPI, IPC suggested a strong causal relationship between lamivudine and hearing loss.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

Lamotrigine

1. DRESS syndrome

Republic of Korea. MFDS has announced that the package insert for lamotrigine has been updated to include Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome as an adverse reaction.

Lamotrigine is an anticonvulsant drug, used for the treatment and prevention of partial and primary generalized tonic-clonic seizures.

During the evaluation process of reports with serious adverse events, KIDS reviewed one fatal case and subsequently suggested a link between the use of lamotrigine and DRESS syndrome.

This recommendation announced by the MFDS was based on results from the investigation of serious adverse events and expert advice.

Reference:

Based on the communication from MFDS and KIDS, Republic of Korea, March 2018

2. Serious immune system reaction

USA. The US Food and Drug Administration (FDA) has requested that the drug labels and prescribing information for lamotrigine (Lamictal®) include a new warning about the risk of hemophagocytic lymphohistiocytosis (HLH).

Lamotrigine is indicated for seizures and bipolar disorder.

Hemophagocytic lymphohistiocytosis (HLH) causes an uncontrolled response by immune system. HLH typically presents as a persistent fever.

Since lamotrigine's authorization approval in 1994, the FDA identified eight cases worldwide of confirmed or suspected HLH associated with the medicine in children and adults. The FDA has determined that there is reasonable evidence to show that lamotrigine caused the HLH in these eight cases based on the timing of events and order in which they occurred.

Reference:

Safety Alerts for Human Medical Products, US FDA, 25 April 2018 (www.fda.gov)

(See WHO Pharmaceuticals Newsletters No.2, 2015: Risk of serious skin disorders in Japan)

Meropenem

Risk of hypokalaemia

India. NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for meropenem is revised to

include the risk of hypokalaemia as an adverse drug reaction.

Meropenem is used for the treatment of nosocomial infections such as septicaemia, febrile neutropenia, intra-abdominal and pelvic infection, and for cystic fibrosis. Between July 2011 and March 2018, NCC-PvPI received 33 ICSRs of hypokalaemia reported with the use of meropenem. A review of cases by the Signal Review Panel (SRP)-PvPI, IPC, suggested a strong causal relationship between meropenem and hypokalaemia.

Reference:

Based on the communication from IPC, NCC-PvPI, India (<http://ipc.nic.in>)

Propofol

Contraindication in pregnant women removed

Japan. MHLW and PMDA have announced that precautions of propofol preparations (Diprivan®) should be revised to remove the contraindication of use during pregnancy. Propofol can be used by pregnant women or women who may be pregnant provided the potential benefits outweigh the risks.

Propofol is indicated for induction and maintenance of general anesthesia.

Propofol is used for therapy in pregnant women in Europe and the United States. For this reason the MHLW requested the PMDA to conduct an investigation into the use of propofol during pregnancy. As a result, PMDA concluded that the above-mentioned revision to safety precautions of propofol is acceptable.

Reference:

Revision of Precautions, MHLW/PMDA, 27 March 2018 (www.pmda.go.jp/english/)

Sevoflurane

Potential risk of bradycardia in children with Down syndrome

Canada. Health Canada has requested that manufacturers of sevoflurane containing products strengthen the existing product safety information to include information about the risk of bradycardia in children with Down syndrome (DS).

Sevoflurane is an anesthetic drug used during surgery or other medical procedures.

Health Canada re-assessed the potential risk of bradycardia with use of sevoflurane in children with DS following evidence that was published since the last safety review in 2014.

Of 17 internationally identified reports of bradycardia in children with DS, there was a link between bradycardia and the use of sevoflurane in three reports.

Health Canada concluded that there is a link between sevoflurane and the risk of bradycardia in children with DS.

Reference:

Summary Safety Review, Health Canada, 9 April 2018 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.3, 2015: Severe low heart rate in children with Down syndrome in Canada)

Sulfasalazine

DRESS syndrome

Republic of Korea. MFDS has announced that the package insert for sulfasalazine has been updated to include DRESS syndrome as an adverse reaction.

Sulfasalazine is a disease-modifying anti-rheumatic drug (DMARD), used for the treatment of rheumatoid arthritis, psoriatic arthritis and arthritis associated with

inflammatory bowel disease.

Following evaluation of serious adverse events, KIDS reviewed one death case and subsequently suggested a link between the use of sulfasalazine and DRESS syndrome.

This recommendation announced by the MFDS was based on investigation results and expert advice.

Reference:

Based on the communication from MFDS and KIDS, Republic of Korea, March 2018

(See WHO Pharmaceuticals Newsletters No. 4, 2017: Risk of Stevens Johnson Syndrome and toxic epidermal necrolysis in India)

Valproate medicines

Contraindicated in women and girls of childbearing potential

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that valproate containing products (Epilim®, Depakote®) must not be used in women or girls of childbearing potential unless a Pregnancy Prevention Programme is in place due to the teratogenic risk.

Valproate medicines are indicated for the treatment of epilepsy and bipolar disorder.

Valproate is highly teratogenic and evidence supports that use in pregnancy leads to physical birth defects and neurodevelopmental disorders.

In March 2017, the European Union conducted a scientific review which examined the available evidence relating to the effectiveness of previous regulatory actions and consulted widely with healthcare professionals and with patients. Previous communications about the risk of neurodevelopmental disorders and the recommendation that women and girls of childbearing potential use effective

contraception had little impact on prescribing. Data from the Clinical Practice and Research Datalink show that pregnancies continue to be exposed to valproate medicines. Additionally, patients have reported that they still are not receiving the necessary information to make an informed decision in many cases.

The review recommended new measures to avoid valproate exposure in pregnancy.

Reference:

Drug Safety Update, MHRA, 24 April 2018 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletters No.3, 2017: Risk of developmental disorders in UK; No. 2, 2016: Risk of abnormal pregnancy outcomes in UK; No. 2, 2015: Risk of abnormal pregnancy outcomes in UK; No. 1, 2015: Further restriction of the valproate use in women and girls in Ireland; No. 5, 2014: Fetal exposure and cognitive impairment in Australia; No.6, 2013: Risk of neurodevelopmental delay in children following maternal use in UK; No. 3, 2013: Contraindicated for pregnant women for prevention of migraine headaches in USA)

Amarasate extract

Anaphylaxis

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has issued a warning about the risk of anaphylaxis with the use of amarasate extract (Calocurb®).

Amarasate extract is a dietary supplement marketed to support weight loss and appetite control.

Medsafe continues to monitor reports of adverse reactions for this product and all other dietary supplements.

Reference:

Safety Information, Medsafe, 9 May 2018
(www.medsafe.govt.nz/)

Obeticholic acid

Risk of serious liver injury

United Kingdom. The MHRA has issued advice to health-care professionals about the risk of serious liver injury in patients with pre-existing moderate or severe liver impairment, taking obeticholic acid (Ocaliva®). Health-care professionals are reminded to adjust dosing according to liver function.

Obeticholic acid is indicated in the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid.

An EU review assessed reports of serious liver injuries and deaths in patients with primary biliary cholangitis with pre-existing moderate or severe liver impairment who were not adequately dose-adjusted. Liver-related adverse events have occurred both early in exposure and after months of treatment. The review concluded that no changes to the product information are required but suggested that health-care professionals should be reminded of the dosing recommendations.

The MHRA has received two Yellow Card reports of hepatobiliary disorders in the UK associated with obeticholic acid. One case was life-threatening and required hospital admission.

Obeticholic acid is subject to additional monitoring, allowing quick identification of new safety information.

Reference:

Drug Safety Update, MHRA, 24 April 2018
(www.gov.uk/mhra)
(See WHO Pharmaceuticals Newsletters No.5, 2017: Risk of serious liver injury in USA)

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 reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 17 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. Signals are first communicated to National Pharmacovigilance Centres through SIGNAL (a restricted document from UMC), before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal. 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. 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.

Interaction between rosuvastatin and ticagrelor resulting in rhabdomyolysis

Dr. Viola Macolić Šarinić*, Croatia

Summary

A potential signal of an interaction between ticagrelor and rosuvastatin leading to rhabdomyolysis was analysed. VigiBase, the WHO global database of individual case safety reports, contained five well-documented reports from five countries, with one very well-described case as a literature report. The patients who developed rhabdomyolysis were high-risk patients, namely elderly with initially an excessive dose of rosuvastatin, and two patients taking ezetimibe as concomitant therapy, which is known to raise rosuvastatin concentration by a factor of 1.2. The cases in VigiBase support the signal of an interaction between ticagrelor and rosuvastatin, especially in high-risk patients. One form of interaction is a worsening of the renal function caused by ticagrelor, resulting in the rise of plasma concentration of rosuvastatin, which then causes rhabdomyolysis. The other possibility, or additional type, can be the pharmacogenomics polymorphism and interaction on the level of the transporters, which can raise the rosuvastatin level. Patients who have developed elevated creatine kinase levels without clinical symptoms and patients with myositis who were also given this medication should be further assessed. If there is a plausible connection established, the possibility that this is indeed an adverse drug reaction as a consequence of an interaction between ticagrelor and rosuvastatin will be much higher.

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Introduction

During a UMC signal detection screening in September 2016 focusing on drug-drug interactions, five unique cases were identified in the WHO global database of individual case safety reports, VigiBase, which indicated an interaction between ticagrelor and rosuvastatin resulting in rhabdomyolysis. Rhabdomyolysis (literally, "dissolution of skeletal muscle") is a syndrome caused by injury to skeletal muscle and involves leakage of large quantities of potentially toxic intracellular contents into plasma. The aetiology of rhabdomyolysis is trauma and muscle compression, infection, metabolic and genetic factors, but it can also be caused by certain drugs and mycotoxins. The multiplicity of potential causes of rhabdomyolysis notwithstanding, the common denominator appears to be disruption of the sarcolemma and release of intracellular myocyte components. In adults, the triad of muscle weakness, myalgias, and dark urine characterizes rhabdomyolysis. Myalgias and generalized muscle weakness are the most common presenting symptoms. Life-threatening renal failure and disseminated intravascular coagulation are serious complications that appear to be more common in adults. Sensitive laboratory markers of myocyte injury include elevated plasma creatine kinase (CK) levels (often more than four to five times above the normal limit).¹

Ticagrelor, co-administered with acetylsalicylic acid, is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes or with a history of myocardial infarction and a high risk of developing an atherothrombotic event. Ticagrelor is a member of the chemical class

cyclopentyltriazolopyrimidines, which is an oral, direct-acting, selective and reversibly-binding P2Y₁₂ receptor antagonist, that prevents ADP-mediated P2Y₁₂ dependent platelet activation and aggregation. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction or stroke. Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrate nucleoside transporter.^{1,2}

Rosuvastatin is indicated for the treatment of hypercholesterolemia in adults, adolescents, and children aged six years or older with primary hypercholesterolemia (type IIa including heterozygous familial hypercholesterolemia) or mixed dyslipidaemia (type IIb) as an adjunct to diet when response to diet and other non-pharmacological treatments (e.g. exercise, weight reduction) is inadequate. It is also indicated for homozygous familial hypercholesterolemia, as an adjunct to diet and other lipid lowering treatments (e.g. low-density lipoprotein (LDL) apheresis) or if such treatments are not appropriate. Another indication is the prevention of cardiovascular events in patients who are estimated to have a high risk for a first such event, as an adjunct to correction of other risk factors. Rosuvastatin is a selective and competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor for cholesterol. The primary site of action of rosuvastatin is the liver, the target organ for lowering cholesterol. Rosuvastatin increases the number of hepatic LDL receptors on the cell surface, enhancing uptake and catabolism of LDL and it inhibits the hepatic synthesis of very-low-density lipoprotein (VLDL), thereby reducing the total number of VLDL and LDL particles.³

Rhabdomyolysis is a well-known adverse drug reaction (ADR) of statins, but for ticagrelor rhabdomyolysis is not listed as an ADR. An interaction between rosuvastatin and ticagrelor is not mentioned in the summary of product characteristics (SPCs) of either drug.^{2,3}

Reports in Vigibase

As of 28 October 2016, Vigibase contained 16 reports with the reaction rhabdomyolysis (MedDRA preferred term) where the suspected medications were ticagrelor and rosuvastatin. The reports were received from five countries: the Netherlands (11 reports), Bulgaria (2), Canada (1), the United States

(1) and Greece (1). The 11 reports from the Netherlands are in fact a single case. This was initially submitted in 2013 as a spontaneous ADR report from a physician. The other ten reports are the same case as the initial one, but from various companies as literature reports⁴ of that Dutch case, and they are therefore duplicates. For the case report from Bulgaria a follow-up report was sent without any new information, so the second report is not counted as valid. Exclusion of these reports resulted in five unique cases, set out in Table 1.

The gender in four reports is male, and in one female. The case of the female patient (case 1) is doubtful, because of the question of whether the patient was actually a woman; she (he?) received as concomitant medications alfuzozin and finasteride, which are indicated in the therapy of prostatic hypertrophy, also mentioned in the patient's medical history. It can be assumed that in this case the gender was wrongly stated, so all these cases concerned males.

In four of them, elderly patients were involved (70, 76, 78 and 82 years), and in one case a 46-year-old male patient experienced rhabdomyolysis, as reported by a physician. Two of the elderly males received the maximum daily dose of 40 mg of rosuvastatin, one received 20 mg, and for the fourth the dose is unknown; the younger patient received 20 mg of rosuvastatin daily. The recommended dose of ticagrelor is 90 mg twice a day. In two case reports the ticagrelor dose is not stated, but it can be assumed that the patients have received the standard dose, as this is the only recommended one. No report gives data about rosuvastatin plasma concentrations, and there is no data that could indicate that the drug concentrations were measured.

The status of the renal function of the patients were not captured or stated, except in the literature case where a rise of creatinine level was observed one week after the introduction of ticagrelor – from 108 to 124 micromole/l, which refers to a decrease in glomerular filtration from 60 ml/min to 52 ml/min. The recommendation for the rosuvastatin dose is that if the glomerular filtration is under 60 ml/min the dose should be 5 mg rosuvastatin a day, and this dose is recommended for patients older than 70 years, as higher doses are more frequently associated with ADRs. In these cases, none of the patients received only 5 mg rosuvastatin per day; instead, high doses were given (20 to 40 mg a day). For the 46-year-old patient the renal function is not recorded but he was taking lisinopril, an ACE inhibitor, which can also alter renal function.

Table 1. Characteristics of case reports in VigiBase of rhabdomyolysis in association with ticagrelor and rosuvastatin interaction

Case	Age/Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Daily dose	Reactions (MedDRA preferred terms)	Time to onset	Dechallenge/Rechallenge	Outcome	Comment
1	76/F	Rosuvastatin, ticagrelor (both S) Ubidecarenone, pantoprazole, acetylsalicylic acid, fluticasone, formoterol, mometasone, salbutamol, ezetimibe, alfuolozine, finasteride (all C)	10-40 mg 180 mg	Acute myocardial infarction, rhabdomyolysis, intentional product misuse	1 month	-/-	Unknown	No information about renal or liver function in medical history. The dose of rosuvastatin was increased around the time that ticagrelor was added. Unknown how long rosuvastatin was used before.
2	82/M	Rosuvastatin, ticagrelor (both I)	-	Drug interaction, rhabdomyolysis, acute kidney injury	-	-/-	Unknown	No information about renal or liver function in medical history.
3	70/M	Rosuvastatin, ticagrelor (both S)	20 mg 180 mg	Rhabdomyolysis	1.5 years after ticagrelor was added to therapy	Yes/-	Recovering	Medical history states hyperthyroidism. No information about renal or liver function in medical history. Patient had used rosuvastatin for many years without ADR. Ticagrelor was added 1.5 years before the elevated CPK (about 2000U/L) was noted.
4	46/M	Lisinopril, rosuvastatin, ticagrelor (all S) Oxycodone, hydrocodone (both C)	10 mg 20 mg 180 mg	Rhabdomyolysis, pain in extremity, walking disability, chest pain, myocardial infarction	1 month after ticagrelor was added to therapy	-/-	Unknown	Patient had been using rosuvastatin for 3 months when ticagrelor was added. Hospital admission due to symptoms. CK levels were between 800 and 1300 while in hospital. Treatment with fluids and CK levels returned to normal. Rosuvastatin was discontinued and ticagrelor and lisinopril were continued.
5	78/M	Rosuvastatin, ticagrelor (both S) Metoprolol, perindopril, omeprazole, ezetimibe (all C)	40mg 180 mg	Acute kidney injury, rhabdomyolysis	1 month after ticagrelor was added to therapy	Yes/-	Recovering	Patient had been using rosuvastatin for 6 years when ticagrelor was added. One week after introduction of ticagrelor, the renal function decreased from 60 ml/min to 52 ml/min. One month after introduction of ticagrelor, the patient developed acute renal failure after 6 days of vomiting and nausea, and developed rhabdomyolysis with an increase of CPK more than 10 000 IU/L.

Two patients used rosuvastatin and ezetimibe at the same time, which increases 1.2 times the AUC of rosuvastatin. Ezetimibe was given to the 72- and 76-year-old patients (cases 1 and 5), who were already taking the highest dose of rosuvastatin (40 mg). In the SPC for rosuvastatin this interaction is mentioned, but in the ezetimibe SPC it is stated that no clinically-significant pharmacokinetic interactions are found if ezetimibe and rosuvastatin are given together.⁵

In cases 3 and 5 the patient had used rosuvastatin for years without complaints at the time ticagrelor was added and after which the symptoms developed. In case 4 the patient had used rosuvastatin for three months when ticagrelor was introduced. The time to onset of the symptoms after start of the combination of rosuvastatin and ticagrelor was one month in three cases, 1.5 years in one case and in one case it is unknown. In the case where the time to onset is unknown only these two drugs are reported (no other concomitant therapy was listed).

Literature and Labelling

For rosuvastatin, cases of rhabdomyolysis were documented during clinical studies and in the postauthorisation phase. The frequency of rhabdomyolysis is described in the SPC of rosuvastatin as a rare ADR (in $\geq 1/10,000$ to $< 1/1,000$ patients). The risk factors for developing ADRs with rosuvastatin are to be an elderly patient (70 years and above) and/or to have renal and liver impairment. The development of the ADR relates to the blood concentration of rosuvastatin, as the higher the concentration, the more likely it is that the patient may develop rhabdomyolysis.³

In clinical studies, ticagrelor was commonly administered with statins, and evidence of a clinically significant adverse interaction was not observed.² For ticagrelor it was noted that in about 30% of treated patients, especially in those older than 75 years, creatinine levels increased (50% and more from the baseline level has been recorded). This is mentioned in the SPC section 4.4 – Special warnings and precautions for use, but worsening (impairment) of the renal function

is not mentioned either in section 4.4, or as an ADR of ticagrelor in section 4.8.² It is not clear from the text if the renal impairment is because of the illness itself (cardiovascular), old age, or if it is a result of the use of ticagrelor, although it is recommended to check the renal function one month after initiating the treatment with ticagrelor. The SPC section 4.2 states that no dose adjustment for ticagrelor is needed in patients with renal impairment, as the primary route of elimination of the drug and its active metabolite is via hepatic metabolism (biliary secretion). In the elderly about 25% higher concentration of ticagrelor was found, but with no clinically significant differences in comparison to younger patients. Caution is needed in patients with severe hepatic impairment², due to a higher possibility of bleeding.

Discussion and Conclusion

The cases identified in VigiBase are related to a possible interaction between the statin rosuvastatin and the platelet aggregation inhibitor ticagrelor, resulting in rhabdomyolysis as an ADR of rosuvastatin, which depends on the plasma concentration of the statin.

For ticagrelor, it is known from clinical studies that it can elevate the creatinine level and this is stated in section 4.4 of the SPC: Special warnings and precautions for use; it is recommended to measure the level of creatinine one month after the initiation of the ticagrelor therapy especially in patients over 75 years of age. In Section 4.8, as an ADR only higher creatinine levels are described but not renal impairment which can lead to some confusion for the prescriber, who cannot find renal impairment as an ADR of ticagrelor, but which is obvious if the creatinine level rises.

The theory behind this interaction is that ticagrelor alters the renal function, resulting in an increased rosuvastatin concentration which can then cause rhabdomyolysis when the critical concentration of rosuvastatin is reached. However, rosuvastatin is mainly eliminated by biliary excretion, with only 10% by renal excretion. Because of this, no general dose adjustment for rosuvastatin is suggested, only in patients with moderate and severe renal impairment. The patient described in the literature report, before he developed rhabdomyolysis, experienced nausea a few days after ticagrelor was introduced, which is a common ADR of this medicine. He vomited for six days, which precipitated acute renal failure, which then led to worsening of the renal failure with rising creatinine, thus causing rhabdomyolysis, which further impaired the renal function.

All patients described had risk factors for developing rhabdomyolysis, as the dose of rosuvastatin was already too high for their age and impaired renal function, and in two cases there was a possible interaction with ezetimibe, which in addition raises

the rosuvastatin plasma concentration. Adding ticagrelor to this condition gave the additional hazard of increasing the rosuvastatin level to a critical one which caused the symptoms of rhabdomyolysis.

The cause of the rise of rosuvastatin concentration in combination with ticagrelor, is not only the raised creatinine level (which is the sign of renal impairment); genetic factors in the metabolism of ticagrelor and rosuvastatin should be taken into account. There is a possible interaction on the level of P-glycoprotein 1 (Pgp), as it has been shown that the digoxin level increases when given together with ticagrelor. The ticagrelor pharmacokinetics are influenced by three genetic loci: SLCO1B1, which codes OATP1B1 transporter activity, CYP3A4 (ticagrelor is also a mild inhibitor of that enzyme), and UGT2B7.⁶ Ticagrelor is not metabolised by CYP2C9.⁴ Rosuvastatin is not metabolised via the cytochrome P450, nor is it an inhibitor or inductor of these enzymes. Rosuvastatin is transported via OATP1B1 coded with the SLCO1B1 gene, the same as ticagrelor. If there is a gene polymorphism the concentration of rosuvastatin can rise.² Theoretically an addition of several genomic alterations could lead to ticagrelor – rosuvastatin interaction, which results in elevated rosuvastatin plasma concentrations, as we know that only 10% of rosuvastatin is eliminated by the kidneys: a genomic polymorphism on the level of Pgp could lead to an increased interaction on the level of Pgp and SLCO1B1. UGT2B7 is important for the metabolism of ticagrelor, which if altered could raise the concentration of ticagrelor, which could then have a higher interaction with rosuvastatin on the level of the transporters: a higher concentration of ticagrelor can interact on the level of Pgp and raise the level of rosuvastatin which can then lead to rhabdomyolysis.

In conclusion, in all cases a too-high dose of rosuvastatin was given to all patients initially – these doses are not recommended in this age group and in patients with impaired renal function. In two cases ezetimibe was given, despite this combination being known to raise rosuvastatin plasma levels. Ticagrelor raises the creatinine level, which appears not to have been checked in four of the patients one month after the introduction of the medicine, despite this being recommended in the SPC. The SPC for ticagrelor is misleading in that nowhere renal impairment is mentioned, but only the rise of creatinine level – which should be read indirectly as a worsening of the renal function after adding ticagrelor. For rosuvastatin it is not recommended to treat patients at all with severe renal impairment, and for moderate impairment a dose of 5 mg is recommended, even though only 10% of the medicine being excreted by the kidneys. In three cases a plausible time association can be found – the ADR appeared about one month after introduction of the combination of these two medicines. After discontinuation of both medicines

the symptoms regressed or disappeared. All patients were at a high risk of developing such a severe ADR, and the combination of rosuvastatin and ticagrelor taken in this high dose led in the end to the development of the symptoms – we can assume that the rosuvastatin concentrations were already high before adding ticagrelor which then rose to critical levels. The interaction may be caused not only by ticagrelor-related renal impairment, but also pharmacogenomics polymorphism which should be taken into account as it could lead to a higher concentration of rosuvastatin.

The reported cases can be seen as a signal for an interaction between ticagrelor and rosuvastatin especially in high-risk patients (elderly, renal impairment, pharmacogenomics polymorphism, interaction with ezetimibe). Cases of raised CK levels without clinical symptoms and patients with myopathy – myositis should also be studied to see if a combination between rosuvastatin and ticagrelor can lead to these ADRs.

References

1. Muscal E, DeGuzman MM. Medscape: Rhabdomyolysis. Jung LK (ed). New York (NY): Medscape. Accessed: January 2017.
2. European Medicines Agency: Summary of Product Characteristics for ticagrelor (Brilique®).

Available from:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf Accessed: December 2016.

3. UK Medicines & Healthcare products Regulatory Agency: Summary of Product Characteristics for rosuvastatin. Available from: <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1486707217805.pdf> Accessed: December 2016.
4. van Vuren AJ, Jong B, Bootsma HPR, van der Veen MJ, Feith G.W. Ticagrelor-induced renal failure leading to statin-induced rhabdomyolysis. *The Netherlands Journal of Medicine*. 2015(73);136-8.
5. UK Medicines & Healthcare products Regulatory Agency: Summary of Product Characteristics for ezetimibe. Available from: <http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1463115553812.pdf> Accessed: December 2016.
6. Varenhost C, Eriksson N, Johansson A, Barratt BJ, Hagstrom E, Akerblom A, et al.: on behalf of PLATO Investigators. Effect of genetic variations on ticagrelor plasma levels and clinical outcome. *European Heart Journal*. 2015(35);1901-12.

Vemurafenib and cardiac failure

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Summary

Vemurafenib is a low molecular weight, orally available, inhibitor of BRAF serine-threonine kinase (a member of the Raf kinase family of growth signal transduction protein kinases). It is one of the medications widely known as tyrosine kinase inhibitors (TKIs) but should be referred to as protein kinase inhibitors (PKIs). Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

In the WHO global database of individual case safety reports (ICSRs), Vigibase there are currently (10 September 2016) 61 ICSRs of cardiac failure in association with vemurafenib. After elimination of suspected duplicates, there are 59 ICSRs of cardiac failure. Vemurafenib was the only drug suspected in 35 cases. Time to onset was reported in 31 cases and ranged from two days to 14 months with a median of eight weeks. The outcome was stated in 42 reports. The patients were reported as recovered or recovering in 26 cases, not recovered in 10 cases

and the outcome was fatal in the remaining six reports. In the reports where the outcome was reported as recovered or recovering, the drug was withdrawn in 13 cases. The cases reported as recovered or recovering after vemurafenib withdrawal are highly suggestive of a drug-induced effect.

In conclusion, although cardiac failure may have other possible causes in some patients in this series, the use of vemurafenib appears the most likely reason.

Introduction

Vemurafenib is a low molecular weight, orally available, inhibitor of BRAF serine-threonine kinase (a member of the Raf kinase family of growth signal transduction protein kinases). Mutations in the BRAF gene which substitute the valine at amino acid position 600 result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that

would normally be required for proliferation.¹ Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. It is one of the medications widely known as tyrosine kinase inhibitors (TKIs) but should be referred to as protein kinase inhibitors because although the earliest drugs in this class were TKIs, they can now be further categorized based upon the amino acid that they phosphorylate: serine, threonine or tyrosine. Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The most common adverse drug reactions (ADR) (>30%) reported with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. Cutaneous squamous cell carcinoma (CuSCC) was very commonly reported and was most commonly treated by local excision. There are warnings in the product information concerning the possible occurrence of severe hypersensitivity and dermatological reactions, QT prolongation, serious ophthalmologic reactions, non-cuSCC, new primary melanomas, liver laboratory abnormalities and mild to severe photosensitivity.¹

Cardiac failure is a condition in which the heart is unable to pump an adequate amount of blood to meet the metabolic and physiological needs of the body. Cases are often classified using the four stages according to the New York Heart Association.² Basic requirements for use of the term, according to CIOMS, include any three of the following:

- dependent oedema,
- raised jugular venous pressure or hepatomegaly in the absence of liver disease,
- signs of pulmonary congestion or effusion,
- rapid heart-rate (>100 beats/min) or gallop rhythm,
- enlarged heart,
- dyspnoea in the absence of pulmonary disease, or
- ejection fraction less than 35 per cent.²

A large number of drugs have been implicated as a cause of cardiac failure. These include anticancer agents such as anthracyclines, mitoxantrone, cyclophosphamide, fluorouracil, capecitabine and trastuzumab; immunomodulating drugs such as interferon- α -2, interleukin-2, infliximab and etanercept; antidiabetic drugs such as rosiglitazone, pioglitazone and troglitazone; antimigraine drugs such as ergotamine and methysergide; appetite suppressants such as fenfluramine, dexfenfluramine and phentermine; tricyclic antidepressants; antipsychotic drugs such as clozapine; antiparkinsonian drugs such as pergolide and cabergoline; NSAIDs,

glucocorticoids; and antifungal drugs such as itraconazole and amphotericin B.³

In WHO-ART, cardiac failure is a preferred term while in MedDRA, the terms which are coded as cardiac failure in WHO-ART such as cardiac failure acute and cardiac failure congestive, ejection fraction decreased and left ventricular dysfunction are separate preferred terms. These are all analysed together in this assessment as cardiac failure.

Reports in VigiBase

As of 10 September 2016, there are 61 individual case safety reports (ICSRs) of cardiac failure in association with vemurafenib in the WHO global database of ICSR, VigiBase. The association has an IC value of 0.22 with an IC025 value of -0.17. After elimination of suspected duplicates, there are 59 cases. The cases were submitted from the United States (26 cases), France (11), Germany (6), Italy (5), Japan (4), United Kingdom (2), and Australia, Canada, the Czech Republic, the Netherlands and Spain (all 1 each). The patients ranged in age from 9 to 88 years with a median of 67 years in the 44 reports in which this information was provided. The gender distribution was 30 males, 24 females and five not specified.

Vemurafenib was the only drug suspected in 35 of the 59 cases. In the remaining 24 cases, cobimetinib was also suspected in 18 cases while loxoprofen, everolimus and methotrexate were also suspected in one case each. Placebo was suspected in two cases and both ifosfamide and a drug not yet accepted in the WHO Drug Dictionary were suspected in the remaining case. Concomitant drugs were reported in 30 cases and included drugs for treatment of cardiovascular disease (16 cases), pain management (16), thrombosis prophylaxis (12), proton pump inhibitors (11), hypolipidaemics (9), and depression (7).

The indication for vemurafenib was stated in 52 of the 59 reports and was malignant and/or metastatic melanoma or just melanoma in 47 cases, neoplasm in three cases and thyroid cancer, probably metastatic, in the remaining two cases. In the seven reports where a reason for use was not stated, melanoma could be inferred in four of the seven cases.

Time to onset was reported in 31 of the 59 ICSR. It ranged from two days to 14 months with a median of eight weeks. The outcome was stated in 42 reports. The patients were reported as recovered or recovering in 26 cases, not recovered in 10 cases and the outcome was fatal in the remaining six reports. In the reports where the outcome was reported as recovered or recovering, the drug was withdrawn in 13 cases, already stopped before onset in three cases, continued in five cases and the action taken with the drug was unknown in five cases. In another report in which the outcome was unknown, the patient recovered from an initial reaction while continuing to take the

drug but then had a second episode after which vemurafenib was withdrawn. In the cases where the patients had not recovered, the drug was withdrawn in four cases, continued in two cases, continued for some time and then withdrawn in two cases and the action taken with the drug was unknown in the remaining two cases. In the six cases where the outcome was fatal, the drug was withdrawn in three cases and the action taken with the drug was unknown in the remaining three cases. The cause of death was disease progression in one case and complications of heart failure in another case but the cause of death in the remaining four cases was not stated.

Other reactions were described in 36 of the reports. These reactions included other cardiac reactions in 13 cases including myocarditis/pericarditis/cardiomyopathy (5 reports) and atrial fibrillation (4), pulmonary reactions in 10 cases including pleural effusion (4), renal impairment and failure in 10 cases, infections in nine cases including pneumonia (7), dyspnoea (8 cases), skin reactions (5 cases), joint and muscle pain (5 cases) and fatigue/malaise (5 cases).

Literature and Labelling

The product literature does not refer to cardiac failure. Currently, the only cardiac events mentioned in the ADR section of the product labels are QT prolongation (EU SmPC) and atrial fibrillation (US FDA label).^{1,4} The EU SmPC does mention that "older patients (≥ 65 years) may be more likely to experience adverse reactions, including cuSCC, decreased appetite, and cardiac disorders."¹

There are no reports in the literature of cardiac failure in association with vemurafenib. There is a report of QT prolongation in association with treatment with vemurafenib in end stage renal disease although the authors assessed that the probability of this being an adverse drug reaction was low.⁵

The product information for another BRAF enzyme inhibitor, dabrafenib, has a warning that dabrafenib in combination with trametinib has been reported to decrease left ventricular ejection fraction (LVEF).⁶ It also lists ejection fraction decreased as a common adverse reaction but this adverse reaction arises from combination with trametinib and not dabrafenib alone.

Discussion and Conclusion

Case reports in VigiBase suggest that there is a signal for the association of vemurafenib and cardiac failure.

There are 59 reports of cardiac failure and vemurafenib was the only drug suspected in 35 of

the cases. In the remaining 24 cases, cobimetinib was also suspected in 18 cases. All 11 reports from France had both vemurafenib and cobimetinib as suspected drugs as did three reports from Germany, two from Italy and one each from the US and the Netherlands. Cobimetinib is also a kinase inhibitor but cobimetinib and vemurafenib target two different kinases in the RAS/RAF/MEK/ERK pathway. In the product information for cobimetinib, there is a warning concerning both the possibility of QT prolongation and advice that a decrease in LVEF from baseline has been reported in patients receiving cobimetinib. Median time to initial onset of events was four months (1-13 months).⁷ It is therefore possible that in those reports where both vemurafenib and cobimetinib are suspected drugs, cobimetinib might be a more likely suspect. In the nine reports in which the patient recovered, both cobimetinib and vemurafenib were withdrawn in four cases, cobimetinib was withdrawn and vemurafenib continued in four cases and cobimetinib withdrawn and the action taken with vemurafenib unknown in the other case. This dechallenge information appears to favour cobimetinib as the more likely drug. In the five reports where the patient had not recovered, both drugs were withdrawn in two cases, both drugs were continued then stopped in one case, vemurafenib was continued and cobimetinib withdrawn in one case and vemurafenib continued and then stopped and cobimetinib withdrawn in the remaining case. This information appears to slightly favour vemurafenib as the most likely drug.

In the remaining six cases in which there was another suspected drug, those drugs mostly do not appear to be a compelling cause. Methotrexate, loxoprofen and everolimus were suspected in one case each. Cardiac failure is not mentioned as an adverse effect of methotrexate and it was withdrawn six months before onset of cardiac failure and does not appear to be a plausible cause. Similarly, cardiac failure is not mentioned as an adverse effect of loxoprofen and it was withdrawn three months before onset of cardiac failure and also does not appear to be a plausible cause. On the other hand, the product information lists congestive cardiac failure as an uncommon adverse effect for everolimus.⁸ There is no information on time to onset and the outcome was fatal so it is difficult to make an attribution in this case. In another report, both ifosfamide and a drug not yet accepted in the WHO Drug Dictionary were suspected. There is no information on the drug not yet accepted but like many anticancer agents, ifosfamide is cardiotoxic but the delay of four months between the withdrawal of these two drugs and the onset of cardiac failure would appear to favour vemurafenib as the most likely cause. Placebo was suspected in the two remaining cases and it is an unlikely cause.

Time to onset was reported in 31 of the 59 ICSRs. It ranged from two days to 14 months with a median of eight weeks. This appears to be

consistent with other case series. As noted above, cardiac failure in association with cobimetinib had a median time to initial onset of four months with a range of 1-13 months.⁷ A case series of cardiac failure in association with tumour necrosis factor antagonists had a median time to onset of 3.5 months with a range of one day to two years.⁹

The outcome was stated in 42 reports. The patients were reported as recovered or recovering in 26 cases, not recovered in 10 cases and the outcome was fatal in the remaining six reports. In the reports where the outcome was reported as

recovered or recovering, the drug was withdrawn in 13 cases, already stopped before onset in three cases, continued in five cases and the action taken with the drug was unknown in five cases. In another report in which the outcome was unknown, the patient recovered from an initial reaction but then had a second episode while continuing to take vemurafenib after which the drug was withdrawn. The 13 cases of recovery after withdrawal of vemurafenib are strong evidence of the drug as the cause.

Table 1. Case overview of ICSRs in VigiBase of cardiac failure in association with vemurafenib

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome
1	/M	None	Cardiac failure congestive, pneumonia	Unknown
2*	/M	Cobimetinib (S)	Ejection fraction decreased	Unknown
3*	/M	Cobimetinib (S)	Ejection fraction decreased	Unknown
4	56/M	Cobimetinib (S) Carvedilol, digoxin (both C)	Ejection fraction decreased	Recovering
5	47/M	Cobimetinib (S)	Cardiac failure, ejection fraction decreased	Not recovered
6	76/F	Cobimetinib (S) Atorvastatin, acetylsalicylic acid, esomeprazole, fusidic acid, paracetamol, prednisone (all C)	Cardiac failure, rhabdomyolysis	Recovered
7	66/F	Cobimetinib (S)	Cardiac failure	Not recovered
8	/-	Cobimetinib (S)	Cardiac failure, wrong technique in product usage process	Died
9	61/M	Cobimetinib (S)	Ejection fraction decreased	Recovered with sequelae
10	67/F	Cobimetinib (S) Paracetamol (C)	Ejection fraction decreased	Recovering
11	41/-	Cobimetinib (S) Bromazepam, esomeprazole, fentanyl, levetiracetam, mirtazapine, paracetamol, potassium (all C)	Ejection fraction decreased	Recovered
12	76/F	Cobimetinib (S) Acenocoumarol, bumetanide, digoxin, metoprolol, nadroparin, spironolactone (all C)	Cardiac failure	Recovered
13	74/F	Acetylsalicylic acid, insulin aspart, insulin glargine, insulin human, rabeprazole, teneligliptin (all C)	Cardiac failure, interstitial lung disease, myocarditis, pleural effusion, pulmonary oedema	Recovered
14	61/M	Meropenem, methylprednisolone, prednisolone, drug name/s not accepted in WHO-DD (all C)	Cardiac failure, acute kidney injury, acute respiratory distress syndrome	Not recovered
15	40/F	Ifosfamide, drug name/s not accepted in WHO-DD (both S) Cloperastine, lorazepam, loxoprofen, metronidazole, potassium aspartate, rilmazafone, drug name/s not accepted in WHO-DD (all C)	Cardiac failure	Recovering
16	67/M	None	Cardiac failure	Not recovered
17	77/M	Cobimetinib (S) Acetylsalicylic acid, betahistine, fenofibrate, pantoprazole, prednisolone, tamsulosin (all C)	Cardiac failure	Not recovered
18	32/F	Cobimetinib (S) Tramadol (C)	Cardiac failure, haemolytic uraemic syndrome acute	Recovered
19**	74/M	Cetirizine, doxazosin, dutasteride, enoxaparin, furosemide, hydrocodone/paracetamol, ibuprofen, levofloxacin, levothyroxine, metolazone, metoprolol, naproxen, paracetamol, serenoa repens, tamsulosin (all C)	Cardiac failure, atrial fibrillation, renal failure	Unknown
20**	74/M	Cetirizine, doxazosin, dutasteride, enoxaparin, furosemide, hydrocodone/paracetamol, ibuprofen, levofloxacin, levothyroxine, metolazone, metoprolol, naproxen, paracetamol, serenoa repens, tamsulosin (all C)	Cardiac failure congestive, atrial fibrillation, generalised oedema, pyrexia, renal failure	Unknown
21	75/F	Cobimetinib (S) Tinzaparin (C)	Cardiac failure, respiratory distress	Died
22	65/M	Cobimetinib (S)	Left ventricular dysfunction	Recovering
23	45/F	Cobimetinib (S)	Ejection fraction decreased	Recovering
24	/M	Setraline (C)	Cardiac failure, bacterial pericarditis, pleuropericarditis	Recovered with sequelae
25	62/M	Cobimetinib (S)	Ejection fraction decreased	Not recovered
26	39/F	Loxoprofen (S) Losartan, metformin, risperidone, drug name/s not accepted in WHO-DD (all C)	Cardiac failure, toxic epidermal necrolysis	Recovered
27	59/M	Cobimetinib (S) Acetylsalicylic acid, prasugrel, ramipril, simvastatin, torasemide (all C)	Ejection fraction decreased, abdominal discomfort, asthenia, back pain, diarrhoea, electrolyte imbalance, fatigue, general physical health deterioration, hepatic enzyme increased, hyperkeratosis, metastases to liver, musculoskeletal chest pain, nausea, vomiting	Unknown but patient died from other causes

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Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome
28	44/F	Cobimetinib (S)	Ejection fraction decreased, erythema nodosum	Not recovered
29	75/M	None	Cardiac failure congestive, metastatic malignant melanoma	Unknown but died of other causes
30	71/F	Placebo (S) Levofloxacin, levothyroxine, lisinopril, macrogol, oxycodone, prochlorperazine, thioctic acid, tocopherol, vitamin b12, warfarin (all C)	Ejection fraction decreased	Recovered
31	75/M	None	Cardiac failure congestive	Not recovered
32	60/M	Placebo (S) Acetylsalicylic acid, amoxicillin /clavulanic acid, atorvastatin, benzonate, codeine/guaifenesin, dutasteride, fentanyl, hydrocodone/paracetamol, loratadine, morphine, nicotine, omeprazole, oxycodone, potassium, prochlorperazine, sertraline, solifenacin, drug name under assessment for WHO-DD (all C)	Left ventricular dysfunction, atrial fibrillation, cardiomyopathy, pericardial effusion, pleural effusion	Recovered
33	72/-	None	Cardiac failure congestive	Unknown
34	84/M	Acenocoumarol, alprazolam, amlodipine, clopidogrel, domperidone, furosemide, glyceryl trinitrate, levofloxacin, levosulpiride, oxygen, paracetamol, ramipril, simvastatin, zolpidem (all C)	Cardiac failure, abdominal distension, arthralgia, blood bilirubin increased, dyspnoea, polymerase chain reaction	Unknown
35	75/F	Bisoprolol, erythromycin, furosemide, insulin lispro, metformin, pantoprazole, phenprocoumon, ramipril, simvastatin, spironolactone, tolterodine, torasemide, drug name under assessment for WHO-DD (all C)	Cardiac failure	Unknown
36	74/F	None	Cardiac failure, electrocardiogram QT prolonged, visual impairment	Recovered
37	-/M	None	Cardiac failure congestive, confusional state, dehydration, fatigue, heart rate increased, hypotension, pneumonia, renal failure, urinary tract infection	Unknown
38	66/M	None	Cardiac failure congestive, musculoskeletal pain, rash	Unknown
39	-/-	None	Cardiac failure congestive, chronic obstructive pulmonary disease, hypertension	Unknown
40	75/F	Acetylsalicylic acid, benzonate, carvedilol, clopidogrel, furosemide, glyceryl trinitrate, hydroxyzine, isosorbide mononitrate, lidocaine, lisinopril, levothyroxine, lorazepam, mesalazine, ondansetron, oxycodone, salbutamol, sertraline, simvastatin, tolterodine, tramadol, zolpidem (all C)	Cardiac failure congestive, angina pectoris, electrocardiogram QT prolonged, myocardial infarction, pneumonia	Recovered with sequelae
41	9/F	Carboplatin, celecoxib, gabapentin, lamotrigine, levetiracetam, levothyroxine, morphine, temozolomide, vincristine (all C)	Cardiac failure, cardiomyopathy, CNS ventriculitis, neoplasm progression, shunt infection, seizure	Died
42	88/M	None	Cardiac failure	Died
43	66/M	Acetylsalicylic acid, atorvastatin, carvedilol, fluticasone, furosemide, lisinopril, pantoprazole, paroxetine, salbutamol, spironolactone (all C)	Cardiac failure congestive, acute kidney injury, pneumonia	Recovered with sequelae
44	-/M	Milrinone (C)	Cardiac failure congestive, acute kidney injury, pneumonia	Unknown
45	73/M	None	Cardiac failure congestive, acute kidney injury, pulmonary oedema	Recovered
46	66/M	Everolimus (S) Ciclosporin, methylprednisolone, mycophenolic acid, tacrolimus (all C)	Cardiac failure, acute coronary syndrome, diffuse alveolar damage, dyspnoea, myocardial ischaemia, opportunistic infection, pulmonary alveolar haemorrhage, pulmonary oedema, respiratory failure, toxicity to various agents	Died
47	61/M	Codeine/paracetamol, dexamethasone, spironolactone, zopiclone (all C)	Cardiac failure acute, acute kidney injury, blood creatinine increased, blood urea increased, dyspnoea, oedema, pleural effusion, renal impairment	Recovered
48	68/-	None	Cardiac failure, asthenia, cardiomyopathy, decreased appetite, dehydration, dyspnoea, left ventricular dysfunction, lower respiratory tract infection, mucosal inflammation, orthopnoea, poor quality sleep, pneumonia, productive cough, renal function test abnormal	Unknown
49	-/M	None	Ejection fraction decreased, cardiac disorder	Unknown
50	-/F	None	Cardiac failure, acute kidney injury	Unknown
51	-/F	None	Cardiac failure congestive, arthralgia, blister, breast pain, breast swelling, chills, diarrhoea, eye pruritus, fatigue, headache, joint swelling, nausea, nipple swelling, oropharyngeal pain, pruritus, rash, sunburn	Recovered

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome
52	-/F	Methotrexate (S) Amitriptyline, amlodipine, ascorbic acid, calcium, clonazepam, duloxetine, esomeprazole, fish oil, furosemide, hydrocodone/paracetamol, leflunomide, lorazepam, losartan, potassium sodium hydrogen citrate, topiramate, verapamil, vitamins (all C)	Cardiac failure acute, bronchitis, pancytopenia, pneumonia	Recovered
53	-/M	Gabapentin, morphine, ondansetron, oxycodone (all C)	Cardiac failure, dehydration, liver function test abnormal	Died
54	50/F	Aciclovir, esomeprazole, furosemide, spironolactone, drug name under assessment for WHO-DD (all C)	Cardiac failure congestive, death, fluid retention, myocardial infarction, pneumonitis, pulmonary embolism, pulmonary oedema	Recovered but died of other causes
55	-/F	None	Left ventricular dysfunction, atrial fibrillation, dyspnoea, hypotension, multiple organ dysfunction syndrome, pneumothorax	Not recovered but died of other causes
56	74/F	None	Cardiac failure	Not recovered
57	77/M	Acetylsalicylic acid, amlodipine, fentanyl, ibuprofen, macrogol, metamizole, metoprolol, morphine, naloxone/tildidine, omeprazole, pantoprazole, pregabalin, ramipril (all C)	Cardiac failure	Recovered
58	-/M	None	Cardiac failure congestive, dyspnoea	Recovered
59	-/M	None	Cardiac failure congestive, arthralgia, decreased appetite, fatigue, nausea, rash, vomiting	Unknown
60	87/F	None	Cardiac failure congestive, atrial fibrillation, pleural effusion	Unknown
61	66/F	Citric acid/potassium bicarbonate/potassium citrate, fenoterol/pratropium, hydrochlorothiazide, phenprocoumon, ramipril, salmeterol, sertraline, simvastatin, tiotropium, torasemide (all C)	Cardiac failure, fatigue, hypertension	Recovered

*Cases 2 and 3 are suspected duplicates

**Cases 19 and 20 are duplicates

Concomitant drugs were reported in 30 cases and included drugs used in a patient population which might be at risk of cardiac failure due to the presence of cardiovascular disease in about half of those cases. In addition, there are an additional five reports in which pre-existing cardiovascular disease is mentioned and these patients are at increased risk of developing cardiac failure. It is also possible that concomitant cardiac reactions may have caused or made a contribution to the cause of the cardiac failure.

There are no reports in the literature of cardiac failure in association with vemurafenib but although cardiac failure may have other possible causes in some patients in this series, the use of vemurafenib appears the most likely reason. This conclusion is strengthened by the observation that nine of the 59 patients were aged 50 years or less, an age group in which cardiac failure is unlikely to occur through natural causes.

References

1. European Medicines Agency. Summary of Product Characteristics for vemurafenib (Zelboraf®). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002409/WC500124317.pdf. Accessed: 14 September 2017.
2. The Council for International Organizations of Medical Sciences (CIOMS). Reporting adverse drug reactions: definitions of terms and criteria for their use. CIOMS, Geneva, 1999. Available from: [https://cioms.ch/wp-](https://cioms.ch/wp-content/uploads/2017/01/reporting_adverse_drug.pdf)

[content/uploads/2017/01/reporting_adverse_drug.pdf](https://cioms.ch/wp-content/uploads/2017/01/reporting_adverse_drug.pdf). Accessed: 14 September 2017.

3. Slordal L, Spigset O. Heart failure induced by noncardiac drugs, *Drug Saf.* 2006; 29:567-86.
4. US Food and Drug Administration. Zelboraf (vemurafenib) Label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202429s0091bl.pdf. Accessed: 25 September 2017.
5. Iddawela M, Crook S, George L, Lakkaraju A, Nanayakkara N, Hunt R, Adam WR. Safety and efficacy of vemurafenib in end stage renal failure. *BMC Cancer.* 2013;13:581.
6. European Medicines Agency. Summary of Product Characteristics for dabrafenib (Tafinlar®). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002604/WC500149671.pdf. Accessed: 4 October 2017.
7. European Medicines Agency. Summary of Product Characteristics for cobimetinib (Cotellic®). Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003960/WC500198563.pdf. Accessed: September 2017.
8. Electronic Medicines Compendium. Summary of Product Characteristics for everolimus (Afinitor®). Available from: <http://www.medicines.org.uk/emc/medicine/22281>. Accessed: September

SIGNAL

2017.
9. Kwon HJ, Cot TR, Cuffe MS, Kramer JM, Braun MM. Case reports of heart failure

after therapy with a tumor necrosis factor antagonist. *Ann Intern Med.* 2003;138:807-11.

Fifteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

24-25 April 2018

WHO, Geneva

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on Pharmacovigilance policy and issues related to the safety and effectiveness of medicinal products. A summary of discussions and key recommendations from the 15th meeting of ACSoMP is provided below.

1. WHO reports

1.1. Safety and Vigilance (SAV): Medicines

WHO's programme of work for 2019–2023: While the standardized approach to pharmacovigilance will continue, there will be more focus on strengthening capacity to promote the safety of medicines, especially in low- and middle-income countries (LMICs). There is to be a focus on country ownership, but with better quality data, faster detection of signals, reduced costs and reduced mortality and morbidity.

Normative work will be boosted in countries by encouraging more consistent engagement in the work of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), as well as continuing close collaboration with the Council for International Organizations of Medical Sciences (CIOMS). The pharmacovigilance toolkit is being updated and expanded. Indicators are being prepared to assess how ready countries are to use new pharmacovigilance products, and the WHO-ISoP pharmacovigilance curriculum is being adapted to a more competency-based model. WHO's training will include a module on ICH approaches for countries that are interested in this.

Technical assistance: The short-term (1–2 years) aim is to gather intelligence on a small number of products and build minimum capacity for surveillance support to 4–6 countries that will use the products. A further short-term project is to pilot a WHO undergraduate curriculum on pharmacovigilance in selected countries, while general support to countries will aim to link pharmacovigilance activities to the regulatory function. In the longer term (5 years) the goal is to scale up the number of countries supported for preparedness and ensure alignment with the Global Benchmarking Tool priority countries, supporting pharmacovigilance goals and strengthening work. Particular aims will be to support countries to link pharmacovigilance to regulation, and to strengthen the use of new technical developments – such as the Web-RADR (Recognising Adverse Drug Reactions) application and electronic health records.

Significant dates: The 41st annual meeting of national pharmacovigilance centres which will take place in Geneva on 5-9 November 2018 will mark the 50th anniversary of the WHO Programme for International Drug Monitoring (PIDM) and the 40th anniversary of the Uppsala Monitoring Centre (UMC) which has provided technical support for the programme since 1978. The year 2018 also marks the 70th anniversary of the creation of WHO.

Summary of Discussions/Recommendations

- A future meeting of the Advisory Committee should include a session on capacity-building. The Advisory Committee called for more emphasis on building competency in pharmacovigilance for medical products.
- In planning and implementing training curricula, WHO should consider the work of ICH, universities, and of professional societies.
- While there is to be a focus on national ownership, a regional approach to pharmacovigilance could be supported where relevant.
- Because of all the data in assessment reports on various products, sharing these reports amongst various stakeholders would greatly increase knowledge to help guide future safety and vigilance efforts. The Advisory Committee agreed to propose protocols to further encourage access to the data that already exist.
- WHO should help direct people to pharmacovigilance data that are publicly available.

1.2. WHO Collaborating Centre for International Drug Monitoring

Milestones: The Uppsala Monitoring Centre (UMC) reported on research milestones, including:

- Investigating variations in risk between the sexes and between different subgroups of patients;
- A pilot study on detecting systematic medication errors in VigiBase, identifying 10 potential safety issues;
- A project in collaboration with Australia's Therapeutic Goods Administration (TGA) and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) to develop and refine methods for de-identifying case narratives through the use of deep neural networks;
- Completion of the Innovative Medicines Initiative's Web-RADR project;
- Complementing the BLIS methodology for predicting indications in electronic medical records with cluster analysis that grouped related medical events, followed by a pilot study;
- Finalization of four modules on signal detection and causality assessment for the UMC distance learning course.

UMC collaboration: It was reported that collaboration is expanding with a number of partner agencies. UMC now has joint user group meetings and training sessions with the MSSO, the maintenance organization for the Medical Dictionary for Regulatory Activities (MedDRA). Most reports to UMC still come from the United States Food and Drug Administration (FDA), but in 2017 about 10% of reports came from China with large and increasing numbers also from India and the Republic of Korea. Many countries are requesting help in developing skills for data analysis and not just data collection. UMC is therefore increasingly focusing its training in this area.

Summary of Discussions/Recommendations

- Now that database system differences, which caused difficulties in the past, are no longer the main problem, UMC should focus more on encouraging countries to work together.
- More work is needed to help countries understand what actions to take when a signal is announced.
- Since UMC functions as the lead WHO technical partner for the PIDM, it is important that ACSoMP plays a role in guiding the work of UMC by reviewing UMC workplans and submitting comments to the UMC board. UMC will continue to share the workplans with WHO, and through WHO, with ACSoMP for input and advice.
- As the situation in many countries is changing fast, there is a need for a long-term strategic view of pharmacovigilance in order to guide investment for change in 10 years' time. In that regard, ACSoMP should consider having a bigger role in reviewing the workplan of WHO's SAV team (and its collaborating centres).
- Institutions responsible for carrying out pharmacovigilance around the world should be helped to have the capacity to do data analysis and make decisions as to what their data show.
- Efforts should be strengthened to help countries obtain tools to make safety reporting easy. The United Arab Emirates used its own resources to launch the generic version of the WEB-RADR app, Zimbabwe also launched an ADR reporting app.
- As other actors develop apps for data reporting, UMC, a WEB-RADR partner, was urged to complete its development of an interface platform so that data from all sources can be gathered.
- Although there are considerable safeguards on data use, commercial enterprises are able to use online search data to build user profiles. Advice should be developed on data privacy, proposing how and when pharmacovigilance data may be used.

2. The Smart Safety Surveillance (3S) project

Background: WHO and the Bill and Melinda Gates Foundation (BMGF) have introduced "Smart Safety Surveillance" (or 3S), which is a risk-based approach to pharmacovigilance (PV) for new products that have not been introduced into reference regulatory markets and therefore no longer possible to draw on the experience of those markets. The 3S project, which was described at the fourteenth meeting of the Advisory Committee, will include piloting a set of key pharmacovigilance principles using selected new products in selected countries.

Aim of the 3S project: The aim is to establish the proof of concept for strategies for building or strengthening pharmacovigilance systems in LMICs. The strategies are to assess product launches over the coming 10 years, the time frame for product launches, anticipated/potential risks with the products, and

capacity for pharmacovigilance in launch countries. Key objectives are to strengthen the functionality of pharmacovigilance systems, to build capacity to analyse safety data, to improve regulatory decisions, and to support collaboration between public health and pharmacovigilance programmes. Key principles of 3S are to leverage product introduction, to focus surveillance initially on areas identified during development and on products with a high-risk profile, to undertake active surveillance to a targeted period of time, to use current standards for safety, and to leverage and build on current harmonization platforms.

Products: Three products have so far been selected for the pilot project – the tuberculosis medicine bedaquiline (BDQ), the malaria medicine tafenoquine (TFQ), and the rotavirus vaccine Rotavac. A shortlist of priority countries has been drawn up and assessments of these are under way in order to select the final set of countries for the pilot. Discussions have been held with WHO's programmes on tuberculosis, malaria and HIV both to fine-tune details of the pilots and to define criteria for selecting countries. A Project Advisory Group has been set up and includes the chairpersons of ACSoMP and the Global Advisory Committee on Vaccine Safety. In addition, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) has received a grant from the BMGF to provide technical support to 3S.

Summary of Discussions/Recommendations

- Experience gained during 3S could be used to address other issues in resource limited settings (such as substandard products). Although the project is geared to individual countries, there may be implications at a regional level.
- Committee members expressed overall support for 3S and for its pilots. Although the activities are centred around specific medicinal products, the purpose of the project would be to build sustainable systems and capacity for pharmacovigilance.
- Although different countries are expected to have different approaches to pharmacovigilance, and with a different focus and priority, the underlying principles must be the same.
- 3S must ensure that patients' privacy is protected when data are gathered.
- Cultural sensitivities will be important, as will the readiness of industry to become involved and the extent of collaboration with WHO and national disease programmes.
- As the 3S project evolves, thought should be given to the future role of UMC and what more it could do.

2.1. Bedaquiline (BDQ)

One of the pilot projects of 3S will focus on the introduction of the new tuberculosis (TB) medicine bedaquiline (BDQ).

Background: Bedaquiline (BDQ) is the first representative of a new class of medicines expected to address the high unmet medical need for new treatment options for pulmonary multidrug-resistant tuberculosis (MDR-TB). FDA has granted accelerated approval to Sirturo (bedaquiline) tablets in the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) as part of combination therapy in adults in 2012. Bedaquiline (BDQ) was authorized in the European Union (EU) in 2013 with a conditional marketing authorization under the trade name Sirturo with the marketing authorization holder (MAH) Janssen-Cilag International. The European Medicines Agency (EMA) recommended granting conditional marketing authorization because, although the data supplied by the applicant showed that the medicine's benefits outweighed its risks, the data are not yet comprehensive. Therefore, additional studies on the use of BDQ should be conducted by the MAH with the final analysis of the data in November 2021. The authorized indication (EMA, FDA) of BDQ is for the treatment of adults with MDR-TB of the lungs, to be always used in combination with other anti-TB medicines.

Conditions of use: WHO issued an interim guidance which provides advice on the inclusion of bedaquiline in the combination therapy of MDR-TB in accordance with the existing WHO Guidelines for the Programmatic Management of Drug-resistant TB (2011 Update).

BDQ as a 3S Project 'candidate': The decision to include BDQ in the 3S pilot project is based on the selection criteria that were developed by WHO (Safety & Vigilance and WHO Global TB Programme (GTB), and under the advice of the WHO ACSoMP. In brief:

- BDQ is being introduced conditionally, as a pilot phase, in some low and middle income countries (LMICs) at the same time as its introduction in high income countries (HICs) with an orphan status. Since MDR-TB incidence is low in HICs, the medicine has been licensed under the orphan-drug approval process; thus LMICs do not have much data on BDQ from HIC to lean on. Monitoring BDQ, within the 3S project in LMICs, will provide the much needed data on BDQ for LMIC-specific use, about

the QT prolongation impact of the medicine in the treatment, all other hitherto unknown adverse events and the implementation of patient inclusion and monitoring in every day practice.

- Nearly 60% of all MDR-TB patients live in LMICs in Asia and Africa. It is critical that robust data on BDQ are available quickly in these settings through 3S and other projects, to support the scale up of BDQ, from pilot to full-access programmes in LMICs.
- Phase II and Phase III trials are unlikely to provide an exhaustive understanding of the safety profile of a medicine, particularly for harms and drug-drug interactions (DDI) that are uncommon, and therefore surveillance of the kind proposed by this initiative will add to current knowledge.

Summary of Discussions/Recommendations

- In many countries data on new medicines are not shared and ways need to be found to encourage sharing.
- National TB programmes should be urged/supported by WHO to collect data and to share these with national regulators, other countries and ultimately with the WHO global database, for mutual learning.

2.2. Tafenoquine (TFQ)

Background: *P. vivax* malaria has a significant public health and economic impact, with millions of clinical infections, primarily in South and South East Asia, Latin America and the horn of Africa. At present primaquine (PRQ) is the only treatment approved for the radical cure (prevention of relapse) of vivax malaria. PRQ is administered as a once-a-day oral dose for 14 days and it is widely accepted that the long dosing leads to reduced compliance and hence reduced clinical efficacy. Alternative treatments with less frequent dosing regimens are needed.

Tafenoquine (TFQ) is an 8-aminoquinoline derivative with activity against the *P. vivax* lifecycle, including hypnozoites. It has the potential to provide alternative treatment in *P. vivax* infections which can be administered as a single dose. Co-administration with another blood schizonticide (chloroquine) will be required for treatment of *P. vivax* malaria as this combination targets both blood and liver stages of infection.

GlaxoSmithKline (GSK) has applied to the Australian Therapeutics Good Administration (TGA) seeking approval of single-dose tafenoquine treatment for the radical cure (prevention of relapse) of *P. vivax* malaria. GSK also plans to progress regulatory filings in other countries in 2018. Approval of TFQ by TGA will likely facilitate registrations in other malaria-endemic countries in the region. However, as there is no prior experience with TFQ in any country for preventing relapse of *P. vivax* malaria, LMICs will not have sufficient post-marketing safety data when TFQ is introduced in their settings and will need to collect and analyse their own data on TFQ for this indication.

Summary of Discussions/Recommendations

- LMICs within the 3S project must be prepared and supported to monitor TFQ to provide the much-needed post-marketing data on TFQ.

2.3. Pharmacovigilance readiness of 3S pilot countries

Indicators: To carry out a baseline assessment of preparedness, a list of indicators was drawn up and approved by ACSoMP in May 2017. The 21 structural indicators aim to show the presence of key pharmacovigilance structures, systems and mechanisms; 15 process indicators aim to show the extent of pharmacovigilance activities; and a set of outcome and impact indicators is used to identify results of interventions and changes as a measure of impact (such as new legislation or restructuring). The status of public health programmes is also considered. Each set of indicators (structural, process, outcome) covers five areas, namely: 1) Policy, law and regulation, 2) System structure and stakeholder coordination, 3) Signal generation and data management, 4) Risk assessment and evaluation, and 5) Risk management, plus communication and commensurate resources needed for the pharmacovigilance system.

Summary of Discussions/Recommendations

- The systematic approach to organizing the project was welcomed.
- On BDQ, there are four issues that need resolution – data need to be collected, data must be shared with the national authorities, national authorities need to share data with VigiBase, and clarification is needed on who is responsible for analysis.
- Ideally all safety data should be channelled through the national PV system to the global database. If a non-governmental organization (NGO) collects data, on behalf of a marketing authorization holder (MAH), a first step could be to urge the NGO to share its data promptly with the government and arrange for the government to share with WHO/UMC.

- It is important for each country to receive all data on products available in that country. As capacity increases and the country is able to analyse its data, it will also benefit from the data that are in VigiBase. The national regulator and pharmacovigilance centre are accountable for the safety of the patients in their country.
- The 3S project anticipates several levels of pharmacovigilance: with only minimal resources, reporting can be strengthened and encouraged, but in countries with more resources, more advanced pharmacovigilance functions could be implemented.
- Since India has some ongoing studies on Rotavac as well as spontaneous reporting, the aim of the Rotavac pilot is to verify safety and build reassurance.
- The core principle for using key products is to strengthen country pharmacovigilance systems and not only to acquire more data.
- The WHO TB programme's active TB drug safety monitoring and management (aDSM) database collates data from settings with poor or nonexistent pharmacovigilance systems. The data in aDSM are in a format that can be easily transferred to other databases.
- WHO should work on proposals to support data sharing between National TB treatment programmes and the Regulator/National PV Centres.

3. Data access

3.1. Proposed access policy for VigiBase

Background: The WHO Collaborating Centre in Uppsala, (UMC) in Sweden manages the global ICSR database, VigiBase, on behalf of WHO and its Member States participating in the WHO Programme for International Drug Monitoring (PIDM). The original agreement between WHO and the Swedish government only mentioned WHO PIDM use of the data, but subsequent WHA and ICDRA recommendations have requested greater openness. As a result, in 2012 ACSoMP had discussed a proposal about making VigiBase data available to the general public. This led to VigiAccess, for broad, high-level public access to summary information from VigiBase. More recently, academic and industry groups, as well as some training organizations who work with WHO, have requested various levels of access. UMC has prepared a proposal on data access policies. The proposal was presented to the committee for review and advice.

The draft data access policy drew attention to the fact that VigiBase information was collected "for the sole purpose of carrying out the pharmacovigilance activities agreed on within the WHO Programme for International Drug Monitoring (PIDM)" and was intended to strengthen capacity for pharmacovigilance and promote the safe use of medicines. The draft policy identified six groups of stakeholders for VigiBase pharmacovigilance data, namely:

- UMC itself and its Signal Review Panel;
- Approved national authorities of WHO Member States who are members of the PIDM;
- academia;
- marketing authorization holders;
- the general public;
- participants in training activities organized by UMC or other WHO collaborating centres within the PIDM.

In addition, the policy proposed five general principles for data use, namely:

- VigiBase contains anonymized information transferred from Member States. Confidential patient and reporter details should be removed before transfer to VigiBase.
- No onward transfer of the ICSRs in VigiBase is allowed.
- Only anonymized information may be made public.
- All attempts to re-identify data subjects from VigiBase data are prohibited.
- Access to VigiBase data requires signature of a valid user licence agreement, including acceptance of a statement on the nature, confidentiality and limitation of use of the data.

Three levels of access (public, intermediate and extensive) were proposed, to balance transparency and patient confidentiality, access to information, academic interest and towards pharmacovigilance obligations of various stakeholders. ACSoMP members were requested to comment on the scope and content of the proposed policy and the proposed levels of access.

Summary of Discussions/Recommendations

- ACSoMP members were generally positive about the proposed policy which would facilitate data access and give clear guidelines.
- Each country supplying data has to comply with its own national laws on data protection as well as the terms of the policy.
- Access to some data fields will need to be blocked. In the EU, to strengthen anonymity, if there are fewer than three reports on an issue, they are described as EU or non-EU with no indication of country.
- The EMA reported that it does not give access to academic enquirers unless they give evidence of ethics approval. All academic requests should go through some kind of process to ensure that the request is serious and the project is worthwhile.
- Enquirers who want to have data from a specific country should be directed to ask the relevant authority in that country as UMC is concerned only with global data and not country-specific data.
- ACSoMP gave their overall approval to the proposed access policy. The proposal will be formally presented to Member States in the upcoming WHO Annual Meeting of Representatives of National Pharmacovigilance Centres for comments and consideration.

3.2. Regional data platforms

Background: Some groups of countries have expressed interest in operating their own regional pharmacovigilance databases with more comprehensive data on regional issues. One argument is that regional databases could encourage countries to contribute data to the global database. In addition, some regional groupings have asked to have access to the full data held by each country in the group including the case narratives. However, such an arrangement would require all countries of a region to have contractual agreements with each other. For instance, not only would sufficient case details for efficient analysis need to be provided, but collaboration agreements between countries would be required for data-sharing to take place, a data access policy would need to be agreed by all, and there would need to be agreement on the process for granting controlled access.

If this were to go ahead, each country in a region would continue to have its own data in its own VigiFlow/other national database, and submit the data to VigiBase. Instead of seeing only a certain limited level of data from other countries via the VigiLyze interface, as today, the proposal is that each country in a defined regional group could in future access a more detailed set of data from countries in the group.

Additionally, some countries with limited capacity for data management have requested all reports from all companies on all medicines. The concern is that countries that have done little data collection and use so far may be overstretched if they receive all global MAH reports.

Summary of Discussions/Recommendations

- The sharing of data as requested by regions is technically feasible. Countries would be able to join their own regional consortium and submit data in order to use regional data. The EMA's Eudravigilance database was described as a model for this. Another example is VigiFlow, originally developed for Swissmedic, to cater for reporting and data sharing between regional centres in the country.
- Any such request by regional groupings for VigiBase data would need to be made at the highest level. This issue should be taken forward by UMC in consultation with WHO.
- There are different views in countries in some regions, so WHO is attempting to obtain ministerial approval from each country before going ahead with this.
- It would be important to know if a country's laws permit the requester to hold the data being requested, in a regional database.
- Since generics manufacturers are the predominant suppliers of medicines to many resource limited countries, safety data from such companies would be particularly relevant in some regional databases.
- It was agreed that a subgroup of ACSoMP members should draw up a short policy statement setting out the issues of collection and management of global MAH data and making some draft proposals that ACSoMP members could then review and contribute to. This topic could be discussed at the WHO meeting of national pharmacovigilance centres.

4. Pharmacovigilance of HIV medicines during pregnancy

4.1. Update on toxicity monitoring of dolutegravir

Members of ACSoMP received a presentation on “Enhancing toxicity monitoring and active safety surveillance during pregnancy for new antiretroviral (ARV) medicines”. As the world is moving towards 30 million people receiving antiretroviral treatment (ART) in 2020, there is a need to transition to optimized ART regimen. With dolutegravir, there are remaining gaps: in efficacy data with regard to use with TB drugs, and in safety data in pregnancy and breastfeeding, and in children. It is necessary to look at population-level data over long term use and review any unexpected complications that may arise.

The HIV programme is learning from past experience with some other ARV medicines which resulted in serious adverse complications that led to policy changes in the use of ARVs (WHO 2010 introduction of tenofovir to replace stavudine, and of efavirenz in 2013 to replace nevirapine in preferred 1st line). As a result, in July 2017 WHO issued new technical guidance on transitioning to new ARVs, with programmatic considerations including a section on monitoring of toxicity. The guidance presents approaches for routine HIV patient monitoring, active ARV toxicity monitoring (CNS, IRIS, long-term toxicities), surveillance through ARV pregnancy registry and surveillance for congenital anomalies as well as monitoring of mother–infant pairs during breastfeeding.

Among countries that have started transitioning to dolutegravir, Brazil has implemented a pharmacovigilance programme. As of August 2017, approximately 52 000 patients were receiving DTG (with an average of 8000 new patients per month) and, of these, some 36 000 had started ART with DTG. The active toxicity monitoring programme included 45 000 patients and found that 3% referred to experiencing an adverse event, although only 79 patients interrupted DTG because of such an event. Regarding safety during pregnancy, very few countries use DTG in 1st line treatment during pregnancy (example, Botswana), while other countries substitute DTG to another ARV, or use DTG ONLY in exceptional clinical situations. The WHO Guidelines released in 2016 cautioned that there were insufficient data for using DTG during pregnancy or breastfeeding and recommended efavirenz (EFV) in combination with tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) as the preferred option in pregnancy. The main sources of data during pregnancy are the Antiretroviral Pregnancy Registry in the USA, the European Pregnancy and Pediatric HIV cohort collaboration, and an active birth outcomes surveillance study - TSEPAMO study, conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana where DTG is used in first-line regimen.

WHO statement and Q&A on potential safety issue related with DTG

It is important to note that since the ACSoMP meeting took place on 24-25 April, WHO was informed by the investigators from the Botswana Tsepamo study in May of a potential safety signal related to neural tube defects in infants born to women taking dolutegravir at the time of conception.

WHO released a statement on 18 May 2018, available at

link: http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf?ua=1.

WHO is proactively engaging with countries and partners in addressing policy and programmatic implications of these findings for national HIV programmes. To inform the discussions and to guide decision-making, WHO has also released a "questions and answers" (Q&A) document, available at link:

<http://www.who.int/hiv/mediacentre/news/dtg-statement/en/>

See other resources below.

WHO and the Tropical Disease Research (TDR) Programme have established a WHO registry for the Epidemiological Surveillance of Drug Safety during Pregnancy AND a central repository for safety evaluation of dolutegravir (general population) to pool data from programmes and studies to get bigger samples more rapidly and be able to analyze toxicity data. A data entry interface for supporting countries to enter their data into the WHO registry for the Epidemiological Surveillance of Drug Safety during Pregnancy was presented to ACSoMP as well as the list of tools available. It includes: a list of standard variables, data dictionary, data entry programme, user guide, newborn surface examination video. WHO has issued important surveillance recommendations –

- to invest in standard and active monitoring of toxicity to generate data and inform future treatment policies, and
- to share data between studies and types of sites into WHO/TDR platforms with a multi country approach to learn quickly and globally.

List of resources that underscore the above text include:

1. WHO 2017 Transition to new antiretrovirals in HIV programmes: <http://www.who.int/hiv/pub/toolkits/transition-to-new-arv/en/>
2. TDR Central registry for epidemiological surveillance of drug safety in pregnancy: http://www.who.int/tdr/research/tb_hiv/drug-safety-pregnancy/en/
3. EMA: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1
4. FDA: <https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm>
5. PEPFAR: <https://www.pepfar.gov/press/releases/282221.htm>
6. USG: US Guidelines notice: <https://aidsinfo.nih.gov/news/2094/statement-on-potential-safety-signal-in-infants-born-to-women-taking-dolutegravir>