

**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 the latest news from the Smart Safety Surveillance (3S) project.

Contents

Regulatory matters

Safety of medicines

Signal

Feature

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Regulatory Matters

| | |
|--|---|
| Amiodarone | 5 |
| Benzocaine | 5 |
| Cladribine | 5 |
| Clarithromycin | 5 |
| Daclizumab..... | 6 |
| Darunavir | 6 |
| Dasatinib..... | 6 |
| Denosumab | 6 |
| Dipeptidyl peptidase-4 (DPP-4) Inhibitor | 7 |
| Eftrenonacog alfa | 7 |
| Everolimus | 7 |
| Fluoroquinolone antibiotics | 7 |
| Granulocyte-colony stimulating factor (G-CSF) drugs | 8 |
| Hydroxyethyl starch solution..... | 8 |
| Ibrutinib..... | 8 |
| Immunosuppressive medicines (azathioprine, ciclosporin, tacrolimus)..... | 8 |
| Infliximab..... | 9 |
| Metronidazole | 9 |
| Pembrolizumab | 9 |
| Tosufloxacin | 9 |
| Valsartan..... | 9 |

Safety of medicines

| | |
|--|----|
| Canagliflozin | 11 |
| Clozapine | 11 |
| Dolutegravir | 11 |
| Erythropoietins..... | 11 |
| Gadolinium based contrast agents (GBCAs) | 12 |
| Hydrochlorothiazide | 12 |
| Hyoscine butylbromide injection | 12 |
| Imatinib | 13 |
| Lysozyme-containing products | 13 |
| Obeticholic acid..... | 13 |

TABLE OF CONTENTS

| | |
|---|----|
| Sodium-glucose cotransporter-2 (SGLT2) inhibitors | 13 |
| Ulipristal acetate | 13 |
| Zoledronic acid..... | 14 |

Signal

| | |
|--|----|
| Agomelatine – Inappropriate schedule of drug administration..... | 15 |
| Inconsistent labelling for drug interactions..... | 16 |

Feature

| | |
|---|----|
| Latest news from the Smart Safety Surveillance (3S) project | 20 |
|---|----|

Amiodarone

Risk of agranulocytosis and leukopenia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for amiodarone (Ancaron®) should be revised to include agranulocytosis and leukopenia as adverse reactions.

Amiodarone is indicated for treatment of ventricular fibrillation, ventricular tachycardia, and heart failure when patients have not responded to other available antiarrhythmics or when alternative agents cannot be used.

A total of three cases associated with agranulocytosis and/or leukopenia were reported in Japan, and a causal relationship with amiodarone could not be excluded for one of these cases.

Based on the investigation of the evidence currently available, MHLW/PMDA have concluded that revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 19 April 2018 (www.pmda.go.jp/english/)

Benzocaine

Risk of blood disorder in infants and children

USA. The US Food and Drug Administration (FDA) has announced that over the counter (OTC) oral medicinal products containing benzocaine (Anbesol®, Orabase®, Orajel®) should not be used to treat infants and children aged less than two years due to risk of blood disorders.

Benzocaine is a local anesthetic contained in some OTC products for the temporary relief of pain due to minor

irritation, soreness, or injury of the mouth and throat.

Benzocaine can cause a condition in which the amount of oxygen carried through the blood is greatly reduced, called methemoglobinemia, which can be life-threatening and result in death.

In addition, manufacturers were requested to change the labels of benzocaine containing products to include: a warning about methemoglobinemia; contraindication in infants and children younger than two years; and revisions to the directions for parents and caregivers.

Reference:
Safety Alerts for Human Medical Products, US FDA, 23 May 2018 (www.fda.gov)

Cladribine

Risk of progressive multifocal leukoencephalopathy (PML)

Japan. MHLW and PMDA have announced that the package insert for cladribine (Leustatin®) should be revised to include progressive multifocal leukoencephalopathy (PML) as a clinically significant adverse reaction.

Cladribine is indicated for hairy cell leukemia and recurrent, relapsing, or refractory indolent B-cell non-Hodgkin's lymphoma including follicular lymphoma, and mantle cell lymphoma.

While there were no reports of PML in Japan however, there were cases of PML reported in patients exposed to cladribine overseas in the previous three fiscal years.

Based on the investigation of the evidence currently available, MHLW/PMDA have concluded that the revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 19 April 2018 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletters No.1, 2018: Risk of progressive multifocal encephalopathy (PML) in UK and Spain)

Clarithromycin

Risk of arrhythmia, myocardial infarction and cardiovascular mortality

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for clarithromycin-containing medicinal products will be updated to reflect findings from observational studies which have identified a rare, short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with clarithromycin.

Clarithromycin is used to treat various bacterial infections.

It is known that clarithromycin has been associated with effects on QT prolongation and cardiac arrhythmias and the product information for clarithromycin provides guidance on use in patients at risk of ventricular arrhythmia and other cardiac conditions.

As part of a routine periodic assessment of clarithromycin-containing medicines by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA), cumulative evidence to date on cardiovascular safety of clarithromycin was reviewed. The PRAC noted that some observational studies have identified a rare, short term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with clarithromycin. It is recommended that consideration of findings should be balanced with known treatment benefits when prescribing clarithromycin, particularly in patients with a high baseline cardiovascular risk.

Reference:
Drug Safety Newsletter, HPRA, June 2018 (www.hpri.ie)

(See WHO Pharmaceuticals Newsletters No.2, 2018: Potential risk of heart problems or death in patients with heart disease in USA)

Daclizumab

Potential risk of immune reactions

Europe. The European Medicines Agency (EMA) has announced that daclizumab (Zinbryta®) is no longer authorized for use in the EU and has been recalled from hospitals and pharmacies due to the risk of serious and potentially fatal immune reactions.

Daclizumab is indicated to treat relapsing forms of multiple sclerosis.

The EMA confirmed that daclizumab poses a risk of serious and potentially fatal immune reactions affecting the brain, liver and other organs. The EMA therefore confirmed its previous conclusion that the risk outweighs the benefit for patients with multiple sclerosis.

On 27 March 2018, the marketing authorisation was withdrawn.

Reference:

EMA, 18 May 2018
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletters No.2, 2018: Immediate suspension: risk of serious inflammatory brain disorders in Europe; No.6, 2017: Risk of serious liver damage in Europe; No.4, 2017: Provisional restrictions for use in Europe)

Darunavir

Potential risk of treatment failure and maternal-to-child transmission of HIV-1

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for products containing darunavir (Prezista®, Rezolsta® and Symtuza®) will be updated to advise against the use of darunavir boosted with

cobicistat during pregnancy due to risk of treatment failure and maternal-to-child transmission of HIV-1.

Darunavir is an antiretroviral medication used to treat and prevent HIV/AIDS. Cobicistat can be co-administered with darunavir as a booster to increase darunavir levels. They are available in combination in some products.

New pharmacokinetic data show mean exposure of darunavir boosted with cobicistat to be lower during the second and third trimesters of pregnancy. Low darunavir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child.

It has been advised that therapy with darunavir/cobicistat should not be initiated during pregnancy, and women who are pregnant and taking darunavir/cobicistat should be switched to an alternative regimen.

A letter has been sent to relevant health-care professionals to inform them of this information.

Reference:

Drug Safety Update, MHRA, 17 July 2018
(www.gov.uk/mhra)

Dasatinib

Risk of nephrotic syndrome

The Netherlands. The product information for dasatinib (Sprycel®) in all EU Member States has been updated to include the risk of nephrotic syndrome.

Dasatinib is used to treat chronic myeloid leukaemia and Philadelphia-chromosome positive acute lymphoblastic leukaemia.

The Netherlands Pharmacovigilance Centre Lareb has received one report of nephrotic syndrome

associated with the use of dasatinib. This concerned a male aged between 11-20 years who developed nephrotic syndrome 27 days after starting dasatinib. The patient recovered one week after withdrawal of dasatinib and fluid intake restriction. Also the European pharmacovigilance database, EudraVigilance, contained seven strongly supportive cases concerning nephrotic syndrome. In addition, there were five cases reported in the literature and a causal relationship between dasatinib and nephrotic syndrome were found in these cases

Reference:

Based on the communication from the Netherlands Pharmacovigilance Centre Lareb, June 2018
(www.lareb.nl/en/)

Denosumab

1. Risk of new primary malignancies

United Kingdom. The MHRA has announced that the product information for denosumab (Xgeva®) has been updated to include the risk of new primary malignancies.

Denosumab is indicated for the prevention of skeletal-related events, such as pathological fracture, and radiation to bone.

The decision to revise the product label for denosumab occurred following findings from a recent review conducted by the EU. An increased rate of new primary malignancies in patients given denosumab compared to those given zoledronic acid was reported when used for the prevention of skeletal-related events with advanced bone malignancies.

Reference:

Drug Safety Update, MHRA, 22 June 2018
(www.gov.uk/mhra)

2. Risk of hypercalcaemia

United Kingdom. The MHRA has announced that the Summary of Product Characteristics for denosumab has been updated to include risk of hypercalcaemia following discontinuation of treatment for giant cell tumour of the bone.

Cases of clinically significant hypercalcaemia complicated by acute renal injury and requiring hospitalization have been reported in a clinical trial of adults and adolescents with giant cell tumour of bone. Cases of rebound hypercalcaemia were reported up to nine months after discontinuation of denosumab.

Reference:
Drug Safety Update, MHRA, 22 June 2018
(www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletters No.3, 2013: Severe hypocalcaemia in Australia; No.1, 2013: Fatal cases of severe symptomatic hypocalcaemia in UK; No.4, 2012: Risk of severe symptomatic hypocalcaemia, including fatal cases in Canada)

Dipeptidyl peptidase-4 (DPP-4) Inhibitor

Risk of pemphigoid

Japan. MHLW and PMDA have announced that the package inserts for omarigliptin (Marizev®), trelagliptin succinate (Zafatek®), and saxagliptin hydrate (Onglyza®) will be revised to include pemphigoid as a clinically significant adverse reaction.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are indicated for type 2 diabetes mellitus.

A total of 19 cases of pemphigoid associated with the use of DPP-4 were reported during the previous three fiscal years. Of the 19 cases, a causal relationship with DPP-4 inhibitors could not be excluded in six cases.

Based on the investigation of the evidence currently

available, MHLW/PMDA concluded that revision of the package inserts was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 19 April 2018
(www.pmda.go.jp/english/)

Eftrenonacog alfa

Risk of shock and anaphylaxis

Japan. MHLW and PMDA have announced that the package insert for eftrenonacog alfa (Alprolix®) should be revised to include shock and anaphylaxis as clinically significant adverse reactions.

Eftrenonacog alfa is used to inhibit bleeding in patients with blood coagulation factor IX deficiency.

One case involving shock and anaphylaxis was reported, and a causal relationship with the product could not be excluded for this case.

Based on the investigation of the evidence currently available, MHLW/PMDA have concluded that the revision of the package insert was necessary.

Reference:
Revision of Precautions, MHLW/PMDA, 19 April 2018
(www.pmda.go.jp/english/)

Everolimus

Risk of impaired wound healing

Japan. MHLW and PMDA have announced that the package insert of everolimus (Afinitor®) should be revised to include impaired wound healing as a clinically significant adverse reaction.

Everolimus is indicated for unresectable or metastatic renal cell carcinoma, and neuroendocrine tumor.

The decision to revise the label followed the revision of the

product label for another everolimus product called Certican®.

Reference:
Revision of Precautions, MHLW/PMDA, 19 April 2018
(www.pmda.go.jp/english/)

Fluoroquinolone antibiotics

Strengthened warnings on the risk of hypoglycaemia and mental health adverse effects

USA. The FDA has announced that the drug labels of fluoroquinolone antibiotics should be strengthened to include coma as a potential outcome of hypoglycaemia, and to list adverse effects related to mental health such as disorientation and agitation.

Fluoroquinolone antibiotics, such as moxifloxacin, delafloxacin, ciprofloxacin, are indicated to treat certain serious bacterial infections.

Most fluoroquinolone antibiotic product labels include a warning on blood sugar disturbances and mental health adverse effects, but the new label changes will add that hypoglycaemia can lead to coma and will also make the mental health adverse effects more prominent and consistent by listing adverse effects such as disturbances in attention, disorientation, and agitation.

Reference:
Safety Alerts for Human Medical Products, US FDA, 10 July 2018 (www.fda.gov)

(See WHO Pharmaceuticals Newsletters No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA; No.3, 2016: Restricting use in USA)

Granulocyte-colony stimulating factor (G-CSF) drugs

Risk of large vessel vasculitis

Japan. MHLW and PMDA have announced that the package inserts of products containing granulocyte-colony stimulating factor (G-CSF) i.e. filgrastim (Gran®, Filgrastim BS®), pegfilgrastim (G-Lasta®), and lenograstim (Neutrogin®) should be revised to include large vessel vasculitis as a clinically significant adverse reaction.

G-CSF products are indicated for prevention of chemotherapy-induced febrile neutropenia and mobilization of hematopoietic stem cells to peripheral blood.

A total of 20 cases involving large vessel vasculitis were reported, and a causal relationship with the products could not be excluded for 14 of these cases.

Based on an investigation of the current available evidence, MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 19 April 2018 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletters No.3, 2014: Risk of Capillary Leak Syndrome (CLS) in Canada)

Hydroxyethyl starch solution

New measures to protect patients against potential kidney injury

Europe. The EMA has announced the decision of the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) that hydroxyethyl starch (HES) solutions for infusion should remain on the market provided

that a combination of additional measures is implemented.

HES solutions for infusion are used for the management of hypovolaemia (low blood volume), where treatment with alternative infusion solutions alone is not considered sufficient.

Because of the risk of kidney injury and mortality, HES solutions for infusion are contraindicated in patients with sepsis or in critically ill patients. In January 2018, PRAC recommended suspending the marketing authorizations because the product continued to be used in those patients. However, the European Commission (EC) requested that the PRAC and the CMDh further consider possible unmet medical needs that could be caused by the suspension.

The CMDh has now concluded that HES solutions for infusion should remain on the market provided that a combination of additional measures is implemented. One of the new measures is a controlled access programme by the marketing authorization holders to ensure that only accredited hospitals will be supplied with the products. Another measure is packaging warnings that remind health-care professionals that these products must not be used in patients with sepsis or kidney impairment or in critically ill patients.

Reference:

EMA, 29 June 2018 (www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletters No.2, 2018: Risk of kidney injury and death in certain patient populations in Europe; No.1, 2015: Contraindications and warnings in Europe and Canada; No.4, 2013: Suspension of licences in UK and new boxed warning in the US)

Ibrutinib

Potential risk of ventricular tachyarrhythmia

Canada. Health Canada has worked with manufacturers to update the product safety information for ibrutinib (Imbruvica®) to include ventricular tachyarrhythmia.

Ibrutinib is indicated for the treatment of bone marrow and white blood cell cancers. It is also used in patients who suffer from refractory chronic graft versus host disease after receiving transplanted tissue from a donor.

Health Canada has received five Canadian reports and examined 150 international reports of ventricular tachyarrhythmia suspected to be linked to ibrutinib.

Health Canada's review concluded that there may be a link between the use of ibrutinib and the risk of ventricular tachyarrhythmia.

Reference:

Summary Safety Review, Health Canada, 26 July 2018 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.6, 2017: Risk of ventricular tachyarrhythmia, hepatitis B reactivation and infection in Australia; No.5, 2017: Reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and opportunistic infections in UK)

Immunosuppressive medicines (azathioprine, ciclosporin, tacrolimus)

No longer contraindicated for use during pregnancy

Japan. MHLW and PMDA have announced that the package inserts for immunosuppressive medicines such as azathioprine (Imuran® and Azanin®), ciclosporin (Sandimmun®), and tacrolimus (Prograf®) should be changed so that use

during pregnancy is no longer a contraindication. The package inserts should include advice on weighing potential therapeutic benefits with risks when used during pregnancy.

The above immunosuppressants are indicated for prophylaxis of organ rejection transplants, myasthenia gravis and rheumatoid arthritis.

The decision to change the labels was based on current medical knowledge and investigations into the latest literature.

Reference:

Revision of Precautions, MHLW/PMDA, 10 July 2018 (www.pmda.go.jp/english/)

Infliximab

Potential risk of linear IgA bullous dermatosis

Canada. Health Canada is working with manufacturers to update the product safety information for infliximab to include the risk of linear IgA bullous dermatosis.

Infliximab is indicated for autoimmune inflammatory conditions such as psoriasis, rheumatoid or psoriatic arthritis, Crohn's disease and ulcerative colitis.

Health Canada received one Canadian report of a blistering skin condition in a patient treated with infliximab and reviewed six case reports provided by the manufacturer of the drug.

Health Canada's review concluded that there may be a link between the use of infliximab and the risk of linear IgA bullous dermatosis.

Reference:

Summary Safety Review, Health Canada, 23 July 2018 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.5, 2015: Risk of non-melanoma skin cancers, particularly in psoriasis patients in Australia)

Metronidazole

Risk of hepatic impairment

Japan. MHLW and PMDA have announced that the package inserts for metronidazole containing products (such as Flagyl®, Lampion®, Rabefine®, and Vonopion®) should be revised to include hepatic impairment as a clinically significant adverse reaction.

Metronidazole is indicated for treatment of infections such as trichomoniasis, anaerobic bacterial infections, infectious enteritis and bacterial vaginosis.

A total of four cases of hepatic impairment were reported, and a causal relationship with metronidazole could not be excluded for two of these cases. In addition, severe hepatotoxicity or acute hepatic failure resulting in mortality was reported in patients with Cockayne's syndrome.

Based on the investigation of the evidence currently available, MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 19 April 2018 (www.pmda.go.jp/english/)

Pembrolizumab

Risk of sclerosing cholangitis

Japan. MHLW and PMDA have announced that the package insert for pembrolizumab (Keytruda®) should be revised to include sclerosing cholangitis as a clinically significant adverse reaction.

Pembrolizumab is indicated for treatment of unresectable melanoma, and treatment of relapsed or refractory classical Hodgkin lymphoma.

A total of seven cases associated with sclerosing cholangitis were reported, including three cases for which

a causal relationship with the pembrolizumab could not be excluded.

Based on the investigation of currently available evidence, MHLW/PMDA concluded that revision of the package insert was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 19 April 2018 (www.pmda.go.jp/english/)

Tosufloxacin

Risk of nephrogenic diabetes insipidus

Japan. MHLW and PMDA have announced that the package insert for tosylfloxacin (Ozex® and Tosuxacin®) should be revised to include nephrogenic diabetes insipidus as a clinically significant adverse reaction.

Tosufloxacin is indicated for superficial skin infections, deep-seated skin infections and chronic pyoderma.

A total of two cases associated with nephrogenic diabetes insipidus were reported, and a causal relationship with the product could not be excluded for these cases.

Based on the investigation of currently available evidence, MHLW/PMDA concluded that revision of the package inserts was necessary.

Reference:

Revision of Precautions, MHLW/PMDA, 19 April 2018 (www.pmda.go.jp/english/)

Valsartan

Recalled due to the contamination with N-nitrosodimethylamine (NDMA)

Europe. The EMA has issued an update on the recall of all valsartan medicines containing the active substance from Zhejiang Huahai Pharmaceuticals from

pharmacies in the EU. The recall occurred after an impurity N-nitrosodimethylamine (NDMA) was found in the active substance.

Valsartan is an angiotensin II receptor antagonist used to treat hypertension, recent heart attack, and heart failure.

NDMA is classified as a probable human carcinogen based on animal tests. It is present in some foods and water supplies but is not expected to cause harm when ingested in very low levels.

The EMA is conducting a review of the possible health effects in patients who may have taken valsartan medicines containing NDMA. A Preliminary estimate of the possible cancer risk based on average levels of this impurity detected in the active substance from Zhejiang Huahai Pharmaceuticals was extrapolated from animal studies.

EMA estimates that there could be one extra case of cancer for every 5,000 patients taking the affected medicines at the highest valsartan dose every day for seven years. The estimate assumes that the NDMA present in the active substance is carried over in the final product in the same amount. Consideration in the context of the lifetime risk of cancer in the EU (1 in 3) and NDMA exposure from other sources should be made.

Companies that had used the active substance from Zhejiang Huahai in their valsartan medicines are required to test samples for actual NDMA levels in the final products.

It is important to note that there is no immediate risk to patients. Patients taking the affected medicines who have not yet switched to an alternative should not stop taking their medicines without consulting their doctor or pharmacist.

Reference:

Based on the communication

from EMA, August 2018
(www.ema.europa.eu)

Canagliflozin

Risk of lower-extremity skin ulcer

Singapore. The Health Sciences Authority (HSA) has advised health-care professionals to consider available safety information when prescribing canagliflozin (Invokana®) and monitor for complications such as lower-extremity skin ulcers which can result in lower limb amputation (LLA).

Canagliflozin is indicated for type 2 diabetes mellitus.

Increased risk of complications leading to LLA in patients exposed to canagliflozin was observed in an ongoing long-term cardiovascular outcome trial, (Canagliflozin Cardiovascular Assessment Study, CANVAS). This was communicated to health-care professionals.

HSA will continue to closely monitor the local and international developments regarding the risk of complications leading to LLA with canagliflozin and other sodium-glucose cotransporter-2 (SGLT2) inhibitors and will update health-care professionals of any new, significant findings.

Reference:

Product Safety Alerts, HSA, 11 May 2018 (<http://www.hsa.gov.sg/>)

(See WHO Pharmaceuticals Newsletters No.1, 2018: Risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure in Chile; No.4, 2017: Increased risk of leg and foot amputations in USA; No.2, 2017: Risk of lower limb amputation in Malaysia; Potential risk of toe amputation in Europe; No.4, 2016: Signal of increased risk of lower extremity amputations in high cardiovascular risk patients in UK; No.3, 2016: Risk of leg and foot amputations: under investigation in USA)

Clozapine

Gastrointestinal effects

Australia. The Therapeutic Goods Administration (TGA)

has issued a reminder to health-care professionals that clozapine is associated with varying degrees of gastrointestinal hypomotility/impaired intestinal peristalsis.

Clozapine is an atypical antipsychotic agent indicated for treatment-resistant schizophrenia.

Clozapine-induced gastrointestinal hypomotility/impaired intestinal peristalsis can lead to severe constipation and potentially fatal outcomes.

A 2017 review of cases reported to TGA and the New Zealand Pharmacovigilance Centre between 1992 and 2013 found 160 cases of serious gastrointestinal hypomotility. The case fatality rate was 18%, with 29 death cases.

TGA recommends close monitoring of bowel function and constipation in patients on clozapine.

Reference:

Medicines Safety Update, TGA, Vol. 9, No. 2, June 2018 (www.tga.gov.au)

(See WHO Pharmaceuticals Newsletters No.6, 2017: Potentially fatal risk of intestinal obstruction, faecal impaction, and paralytic ileus in UK)

Dolutegravir

Potential risk of neural tube birth defects

1. USA. The FDA has issued an alert to the public about reports of serious neural tube birth defects involving the brain, spine, and spinal cord in babies born to women treated with dolutegravir (Juluca®, Tivicay®, and Triumeq®).

Dolutegravir is an antiretroviral medicine used in combination with other antiretroviral medicines to treat human immunodeficiency virus (HIV).

The FDA recommends that patients should not stop taking dolutegravir without talking to their prescribers as stopping

the medicine can cause the HIV infection to worsen.

The FDA recommends that health-care professionals should inform women of childbearing age about the potential risk of neural tube defects.

Reference:

Safety Alerts for Human Medical Products, US FDA, 18 May 2018 (www.fda.gov)

2. Europe. The EMA has announced that the HIV medicine dolutegravir should not be used in women seeking to become pregnant and advises that women of child bearing age should use effective contraception while taking dolutegravir.

The EMA is evaluating preliminary results from a study that examined babies born to 11,558 HIV-infected women in Botswana, and showed that 0.9% of babies (4 of 426) whose mothers became pregnant while taking dolutegravir had a neural tube defect, compared with 0.1% of babies (14 of 11,173) whose mothers took other HIV medicines.

Reference:

EMA, 18 May 2018 (www.ema.europa.eu)

Also, WHO issued a statement on dolutegravir on 18 May, 2018.

Reference:

Full List of WHO Medical Product Alerts, WHO, 18 May 2018 (http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf?ua=1)

Erythropoietins

Risk of severe cutaneous adverse reactions (SCAR)

Singapore. The HSA has informed health-care professionals that severe cutaneous adverse reactions (SCAR) including Stevens-

Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), have been reported overseas in patients treated with recombinant human erythropoietins (r-HuEPOs).

R-HuEPOs are a class of biologics generally used for the treatment of anaemia associated with chronic renal failure.

The HSA has referred to the EMA's review on SCAR associated with r-HuEPOs, where 23 reports of SJS and 14 reports of TEN with r-HuEPOs were identified. Among them, a causal association was found for eight reports of SJS and one case of TEN.

Although HSA did not receive any local report of SCAR, health-care professionals are advised to educate their patients on the early recognition of signs and symptoms of allergic reactions, and the importance of prompt withdrawal of r-HuEPOs if signs and symptoms are presented.

Reference:

Product Safety Alerts, HSA, 11 May 2018 (<http://www.hsa.gov.sg>)

(See WHO Pharmaceuticals Newsletters No.1, 2018: Risk of Severe Cutaneous Adverse Reactions (SCARs) in Ireland and in UK)

Gadolinium based contrast agents (GBCAs)

Risk of gadolinium brain deposits

Singapore. The HSA has advised health-care professionals to use the lowest effective dose of Gadolinium based contrast agents (GBCAs) e.g. Gadoteric acid (Dotarem®) whenever possible.

GBCAs are generally indicated for the enhancement of magnetic resonance image (MRI) scans of several anatomical structures.

The HSA has not received any reports of adverse events arising from the accumulation of gadolinium in brain tissues.

The HSA's review concluded that while there is no definite evidence of clinical harm of gadolinium brain deposition following GBCA administration, health-care professionals are advised to use the lowest effective dose of GBCA whenever possible as a precautionary measure.

Reference:

Product Safety Alerts, HSA, 11 May 2018 (<http://www.hsa.gov.sg>)

(See WHO Pharmaceuticals Newsletters No.3, 2018: Potential neurological adverse effects in Canada; 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 in 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)

Hydrochlorothiazide

Potential Risk of hearing disorders

Eritrea. The Eritrean Pharmacovigilance Centre has reviewed cases of hearing disorders reported with the use of hydrochlorothiazide and concluded that there is a suggestive causal relationship.

Hydrochlorothiazide is a diuretic used to treat hypertension and swelling due to fluid build-up.

The Eritrean Pharmacovigilance Centre received cases of hearing disorders, including irreversible deafness associated with hydrochlorothiazide use. Data was retrieved from the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase™.

From 1972 to 2017, 94 cases were submitted from 18 countries to VigiBase™. Twenty-six cases reported hearing disorder following the

sole intake of hydrochlorothiazide. Consistency and a dose-response relationship were also observed in the case series.

This case series assessment found a suggestive causal relationship between hydrochlorothiazide and hearing disorders, although the results should be interpreted with caution due to study limitations.

Reference:

Based on the communication from Eritrean Pharmacovigilance Centre, July 2018 (www.lareb.nl/en/)

Hyoscine butylbromide injection

Risk of cardiovascular adverse reactions

New Zealand. Medsafe issued an alert warning health-care professionals that hyoscine butylbromide (Buscopan®) injection can lead to cardiovascular adverse reactions, such as hypotension and tachycardia.

Hyoscine butylbromide is used to treat muscle spasm in the gastrointestinal tract.

Internationally, there are fatal reports of patients who received intravenous or intramuscular injection of hyoscine butylbromide.

In New Zealand, the Centre for Adverse Reaction Monitoring (CARM) received nine reports of suspected cardiovascular adverse reactions to hyoscine butylbromide injection between 2013 and 2017.

Medsafe warns that hyoscine butylbromide injection should be used with caution in patients with underlying cardiovascular disease.

Reference:

Prescriber Update, Medsafe, June 2018 (www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletters No.5, 2017: *Caution of use in patients with pre-existing cardiac conditions in Australia*; No.2, 2017: *Risk of serious adverse effects in patients with underlying cardiac disease in UK*)

Imatinib

Potential risk of tendon disorders

Canada. Health Canada has concluded that current evidence does not confirm a link between the use of imatinib (Gleevec®) and the risk of tendon disorders.

Imatinib is indicated to treat several solid tumours such as tumours of the gastrointestinal tract, or blood cancers such as chronic myeloid leukemia.

Health Canada reviewed the potential risk of tendon disorders with the use of imatinib based on six Canadian and 36 international reports, but could not conclude whether the tendon disorders were caused by imatinib.

Reference:

Summary Safety Review, Health Canada, 8 June 2018 (www.hc-sc.gc.ca)

Lysozyme-containing products

Risk of allergic reactions in patients with egg allergies

Singapore. The HSA has announced that lysozyme-containing products have the potential to cause allergic reactions in patients with egg allergies.

Lysozyme containing products are approved as an expectorant and mucolytic for chronic sinusitis as well as treatment for bleeding.

HSA has recently received a report of severe cough, urticaria and eczema flare in a child who was given a lysozyme containing product

and with a known allergy to egg.

Health-care professionals are advised to check if their patients have a history of egg allergy before prescribing or dispensing lysozyme-containing products to their patients.

Reference:

Product Safety Alerts, HSA, 11 May 2018 (<http://www.hsa.gov.sg/>)

Obeticholic acid

Risk of serious liver injury

Ireland. The HPRA has called on health-care professionals to report suspected adverse reactions associated with obeticholic acid (Ocaliva®) use to the HPRA.

Obeticholic acid is indicated to treat primary biliary cholangitis.

Patients with pre-existing moderate or severe liver impairment who are taking obeticholic acid are at risk of serious liver injury; and adequate dose reduction in these patients is therefore essential.

Reference:

Drug Safety Newsletter, HPRA, June 2018 (www.hpra.ie)

(See WHO Pharmaceuticals Newsletters No.3, 2018: *Risk of serious liver injury in UK*; No.5, 2017: *Risk of serious liver injury in USA*)

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Potential risk of acute pancreatitis

Canada. Health Canada has concluded that there is a possible link between the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors such as canagliflozin (Invokana® and Sulisent®), dapagliflozin (Forxiga®), and empagliflozin (Jardiance®) and acute pancreatitis following a

review of the available evidence.

SGLT2 inhibitors are used to lower blood sugar in patients with type 2 diabetes.

Health Canada received 20 Canadian reports and examined 28 international reports of acute pancreatitis related to the use of SGLT2 inhibitors.

Health Canada's review concluded that there may be a link between the use of SGLT2 inhibitors and acute pancreatitis. Health Canada is working with the manufacturers to update the product safety information on SGLT2 inhibitors to inform health-care professionals about this risk.

Reference:

Summary Safety Review, Health Canada, 20 July 2018 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.1, 2018: *Risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure in Chile*; No.6, 2015: *Risk of acute kidney injury in Canada*)

Ulipristal acetate

New measures to minimise the risk of liver injury

Europe. The EMA has issued new measures to minimize risk of rare but serious liver injury with the use of ulipristal acetate (Esmya®).

Ulipristal acetate is indicated for the treatment of moderate to severe symptoms of uterine fibroids.

EMA's PRAC reviewed reports of serious liver injury, and concluded that ulipristal use may have contributed to these cases. Therefore, the PRAC recommends that use of ulipristal should be restricted.

The restrictive measures include contraindicating use in women with known liver problems, and performing liver tests before, during and after stopping treatment.

The PRAC's recommendations will be sent to the European Commission for a final legal decision.

Reference:

EMA, 1 June 2018
(www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletters No.2, 2018: Potential risk of liver injury in Europe)

Zoledronic acid

Risk of hypocalcaemia

New Zealand. Medsafe has issued advice to reduce the risk of hypocalcaemia with the use of zoledronic acid (Zometa®) injection.

Zoledronic acid is indicated for prevention of skeletal-related events in patients with advanced malignancies involving bone, and treatment of tumour-induced hypercalcaemia, Paget's disease and osteoporosis.

CARM received ten reports of hypocalcaemia with zoledronic acid. One case was fatal.

Medsafe advises measuring serum calcium and adequately supplementing calcium and vitamin D during therapy.

Reference:

Prescriber Update, Medsafe, June 2018
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletters No.4, 2012: Osteonecrosis of the Jaw (ONJ) in New Zealand)

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 (page 19). 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.

Agomelatine – Inappropriate schedule of drug administration

Alem Zekarias, Uppsala Monitoring Centre

Agomelatine is a MT₁ and MT₂ melatonin receptor agonist, and a serotonin (5-HT_{2c}) antagonist. It is approved in Europe, Australia and Latin America for the treatment of major depression in adults. The efficacy and safety of agomelatine have been established in elderly depressed patients over 75 years of age, but clinical data showed no effect. Therefore, agomelatine should not be used by patients older than 75 years. The recommended dose is 25 mg once daily taken orally at bedtime. If there is no improvement of symptoms after a couple of weeks, the dose may be increased to 50 mg once daily, i.e. two 25 mg tablets taken at the same time at bedtime.^{1,2}

In VigiBase, the WHO global database of individual case safety reports, as of January 2018 there are seven reports on agomelatine and inappropriate schedule of drug administration, leading to adverse drug reactions (ADRs). The reports were submitted from Germany (four reports), Belgium, Greece and Switzerland (one report each). In three reports, in which the indications were insomnia, malaise, depression and burnout syndrome, the patients had taken the drug in the morning or in the early afternoon instead of at bedtime as recommended. In addition, one of these patients was 80 years old. These patients developed dizziness, tiredness and presented with slowing of movement which affected daily life. Four out of seven reports are briefly discussed below, as the remaining three do not provide any information on the time of intake.

A 48-year old man with medical history of depression had taken agomelatine 25 mg daily in

the morning since April 2013. After three weeks, he experienced back and chest pain, episodes of migraine and dizziness. The events affected his daily activities including his ability to drive. In July 2013, the drug was discontinued, and the events resolved.

A 45-year old man with burnout symptoms had been taking agomelatine 25 mg daily in the morning since October 2012. After his first intake of the drug, he started to feel tired and later had a car accident due to microsleep.

A 72-year old man treated with agomelatine since June 2014 for insomnia started to feel agitated and restless one month into the treatment. Agomelatine was reduced to 12.5 mg per day taken in the early afternoon. As the patient still experienced mild tiredness, the drug was stopped in December 2014 and the patient recovered. A positive rechallenge occurred three months later. Agomelatine was withdrawn in mid-April 2015 and the patient recovered within a week.

A fourth report mentioned both an inappropriate administration schedule (as the drug was taken in the morning) and off-label use, as the patient was 80-years old.^{1,2}

The Summary of Product Characteristics for agomelatine states that the drug should be taken at bedtime independent of dose due to its neurological effects.^{1,2} Several cases in VigiBase document that intake at a different time of the day can lead to significant ADRs.

References

1. European Medicines Agency: Summary of Product Characteristics for valdoxan. Available from: <https://www2.medicines.org.uk/emc/medicine/21830>. Accessed: January 2018.
2. European Medicines Agency: Product

Information Leaflet for valdoxan. Available from: <https://www2.medicines.org.uk/emc/medicine/21841>. Accessed: January 2018

Inconsistent labelling for drug interactions

Sofia Zappacosta, Sarah Watson and Marian Attalla, Uppsala Monitoring Centre

During a signal detection screening focusing on interactions, four drug-drug-adverse drug reaction (ADR) combinations were highlighted in VigiBase, the WHO global database of individual case safety reports. The case series for the combinations presented here are not signals *per se*, however they reveal labelling inconsistencies regarding the interaction information in the available product information issued by the Food and Drug Administration (FDA) in the United States (US), the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) and the European Medicines Agency (EMA) in the European Union (EU). The 'inconsistencies' refer to differences in the information provided by these regulatory agencies, being incomplete or contradictory. A drug-drug-ADR interaction was considered labelled when the interaction was mentioned in at least one of the sources of the interacting drugs. Ideally, the interaction and the potential ADRs caused by it should be mentioned for both interacting drugs in the US FDA label and the UK Summary of Product Characteristics (SmPC) if the drugs are marketed in both countries.

Metformin – ciprofloxacin/levofloxacin and hypoglycaemia

Metformin is a well-known antidiabetic agent from the group of biguanides. It is believed not to cause hypoglycaemia in monotherapy, but can do so if combined with other oral antidiabetic drugs or insulin.¹ Ciprofloxacin and levofloxacin, both antibacterial agents from the group of fluoroquinolones, have not been shown to cause hypoglycaemia when administered alone in the treatment of bacterial infections.^{2,3} As of 10 November 2017, there were 32 reports where metformin and ciprofloxacin or levofloxacin were co-reported as suspected or interacting related to hypoglycaemic effects in VigiBase.

The reports support the FDA warning of the potential risk of the interaction between antidiabetic agents and ciprofloxacin or levofloxacin. These fluoroquinolones may intensify the action of

metformin. The warning is present in the FDA labels for the antibacterial agents but not in the label for metformin.^{1,2,3} When looking at the UK SmPC, there is no mention of the ciprofloxacin or levofloxacin interaction in the metformin label. The warning regarding the interaction is only present in the levofloxacin SmPC.^{4,5,6}

Sertraline – quetiapine and serotonin syndrome

Sertraline is a selective serotonin reuptake inhibitor (SSRI) indicated for the treatment of depressive episodes, panic disorder, obsessive compulsive disorder, social anxiety disorder and post-traumatic stress disorder.⁷ Quetiapine is an atypical antipsychotic agent with affinity for brain serotonin and dopamine D1- and D2-receptors. It is indicated for the treatment of schizophrenia, bipolar disorder and as an add-on treatment of major depressive episodes in patients with major depressive disorder.⁸ Sertraline has been described to cause serotonin syndrome (SS), a potentially life-threatening condition whose signs and symptoms may include mental status changes, seizures, neuromuscular symptoms.⁷ The development of neuroleptic malignant syndrome (NMS) has also been reported with SSRIs, including treatment with sertraline. NMS is characterized by similar symptoms to SS, such as altered mental status, muscular rigidity and tremor. As of 10 November 2017, there were 29 reports where sertraline and quetiapine were co-reported as suspected or interacting drugs related to SS, and 15 reports for NMS. The risk of developing SS or NMS increases when concomitant antipsychotics such as quetiapine are administered to patients using sertraline, as described in the UK SmPC for sertraline.⁹ The antipsychotic quetiapine on its own has also been reported to cause NMS.¹⁰ Interestingly, no mention of an increased risk of SS is present in neither of the labels for quetiapine when used in combination with sertraline.^{8,10}

Tacrolimus – mycophenolic acid and drug level increased

Tacrolimus and mycophenolic acid are highly potent immunosuppressive agents, indicated for the prophylaxis of acute transplant rejection.^{11,12} Mycophenolic acid is indicated in combination with ciclosporin and corticosteroids.¹³ As of 10 November 2017, there were 24 reports in VigiBase in which tacrolimus and mycophenolic acid were reported as suspected or interacting drugs with respect to the adverse event “drug level increased”. In the UK SmPC for mycophenolic acid, it is mentioned that the drug exposure of mycophenolic acid may increase when administered concurrently with tacrolimus (compared to when it is administered with ciclosporin).¹³ It is also stated that clinicians should note this increase and adjust the dose of mycophenolic acid according to the situation. However, the UK SmPC for tacrolimus does not mention this interaction.¹⁴ On the other hand, this interaction is given by the FDA for tacrolimus but not for mycophenolic acid.^{11,12}

Acetylsalicylic acid – dipyridamole and melaena

Acetylsalicylic acid (ASA) is broadly used in sporadic or continuous treatments for various indications because of its analgesic, anti-inflammatory, anti-pyretic and uricosuric actions.¹⁵ Dipyridamole, a platelet aggregation inhibitor, is indicated as an adjunct to oral anti-coagulation in the prevention of postoperative thromboembolic complications of cardiac valve replacement.¹⁶ Melaena describes dark (tarry), faeces containing partly digested blood, as a result of internal bleeding or the swallowing of blood.¹⁷ The treatment with ASA and dipyridamole is available as a combination pill in the US and the EU for the secondary prevention of ischaemic stroke and for prophylaxis of thromboembolism associated with prosthetic heart valves. The combination treatment includes a small 25 mg dose of ASA with 200 mg of dipyridamole.^{18,19} As of 10 November 2017, there were 30 reports in VigiBase in which the drugs are reported as suspected or interacting with melaena. The number of reports increases to 85 when adding the term gastrointestinal haemorrhage.

The US label for the combination pill mentions an “increased risk of bleeding” when using ASA and extended-release dipyridamole.¹⁹ The UK SmPC for the combination pill, on the contrary, says that the addition of dipyridamole to ASA does not increase the incidence of bleeding events, when these two substances are combined.¹⁸

However, the UK SmPC for ASA (75 mg) mentions that an increased risk of gastrointestinal bleeding is present when concomitant anti-platelet agents such

as dipyridamole are used.²⁰ Similarly, the US ASA label also mentions the increased risk when using ASA with anti-coagulants, but no specific mention of dipyridamole is described.¹⁵ The inconsistency is strengthened when looking at the dipyridamole labels: the US label does not mention the risk of bleeding and the UK SmPC mentions that the concomitant use with ASA does not increase the risk of bleeding.^{16,21}

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5. European Medicines Agency: Summary of Product Characteristics for ciprofloxacin. Available from: <http://www.medicines.org.uk/emc/medicine/20345> Accessed: November 2017.
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CAVEAT DOCUMENT

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

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). The information is stored in VigiBase, the WHO international database of suspected adverse drug reactions (ADRs). It is important to understand the limitations and qualifications that apply to this information and its use.

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

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

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

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

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

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

Confidential data

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

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

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

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

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

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

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Latest news from the Smart Safety Surveillance (3S) project

In September 2016, WHO signed a grant agreement with the Bill and Melinda Gates Foundation on the Smart Safety Surveillance (3S) project. The project proposes strengthening of pharmacovigilance (PV) systems and practices in selected low and middle income countries, to support the introduction of new health products through the identification, assessment, and management of any risks associated with them. In 2017, the Medicines and Healthcare products Regulatory Agency (MHRA), UK signed up as a technical partner and is working in collaboration with WHO to provide PV technical support to countries.

An insight into the PV system in Armenia was gathered following an initial mission by WHO to Armenia in March 2018¹. WHO and the MHRA have worked together on a work plan to address identified gaps and needs with the aim of strengthening the PV systems in countries. The work package was launched in July 11-13 through a joint WHO and MHRA mission. Below is an account of the mission by Mick Foy, Head of Pharmacovigilance Strategy, Vigilance Intelligence and Research Group, Medicines Healthcare products Agency (MHRA), UK.

3S Goes Live in Armenia

The Smart Safety Surveillance (3S) project got under way in Armenia 11-13 July when MHRA and WHO HQ colleagues from the Safety and Vigilance team travelled to Yerevan to scope out a package of activities to strengthen the safety monitoring of bedaquiline and the national pharmacovigilance system in general.

The three day meeting, Chaired by WHO HQ, met with the Deputy Health Minister, Anahit Avanesyan and senior leaders from the Ministry of Health and the National Regulatory Agency of Armenia. The first day was a great opportunity to

explain to the Deputy Minister, the Head of the Department of Drugs, the Director of the National Agency and other distinguished colleagues about 3S and how the team would work with National agencies to enhance pharmacovigilance systems and in particular the monitoring of the pathfinder drugs such as bedaquiline.

The second day focussed on working directly with the pharmacovigilance team in Armenia to agree a set of activities to deliver on the 3S objectives. These cover the entire pharmacovigilance lifecycle from active surveillance on bedaquiline, and adverse drug reaction (ADR) data collection to analysis and communication of risk, all framed within a robust set of regulations.

We also met with officials from Médecins Sans Frontières who are heavily involved in the TB programme in Armenia and have collected data on bedaquiline which will be important to add to the national PV database and VigiBase.

After feeding back to the Deputy Minister on day three the visiting team left Yerevan with a comprehensive set of goals for the 3S project in Armenia, to deliver on immediately.

The 3S team from WHO and MHRA are looking forward to a productive partnership.



¹ Feature: Enhancing Pharmacovigilance in Low and Middle Income Countries using Smart Safety Surveillance, WHO Pharmaceuticals Newsletter: 2018, Issue 2



5th Asia Pacific Pharmacovigilance Training Course (Building Capacity in Pharmacovigilance)



Training Course hosted by
Indian Pharmacopoeia Commission
in collaboration with Uppsala Monitoring Centre, Sweden
4th – 15th March 2019

About the Course

Indian Pharmacopoeia Commission is hosting the 5th Asia Pacific Pharmacovigilance Training Course at Indian Pharmacopoeia Commission (IPC), Ghaziabad (Delhi - National Capital Region), India from 4th -15th March 2019 in collaboration with Uppsala Monitoring Centre, Sweden.

For the first time this highly informative training course is conducted at IPC, Ghaziabad, India, a WHO Collaborating Centre for Pharmacovigilance in public health programmes and regulatory services.

This course offers a comprehensive pharmacovigilance programme to about 30 Pharmacovigilance professionals each year. The previous training courses took place at the JSS University, Mysuru in February 2015, January 2016, January 2017 & January 2018.

Training Methodology

The course offers creative, interactive and relevant sessions to ensure participants are actively engaged from the outset.

The course uses a combination of instructions, group discussion, case studies, and field visits.

Course Benefits

The course helps participants to improve their pharmacovigilance skills and expertise. Issues related to burden of ADRs, communications, risk management and fund raising in Pharmacovigilance are covered.



Length of Course: Two Weeks



Course Location:
*Indian Pharmacopoeia Commission,
Ghaziabad (Delhi-NCR), India*



Online Registration:
*Registration Format available at
<http://www.5thasiapacificvtraining.com>*

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For more information kindly visit: <http://www.5thasiapacificvtraining.com>