

**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 edition of the Newsletter includes the recommendations from the 16<sup>th</sup> meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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## Cefepime

### Risk of urticaria

**India.** The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopoeia Commission (IPC) has advised the Central Drugs Standard Control Organisation (CDSCO) to revise the patient information leaflet (PIL) for cefepime to include urticaria as an adverse drug reaction.

Cefepime is indicated for the treatment of pneumonia, bacterial septicaemia, bronchitis, respiratory and urinary tract infections. Between July 2011 and December 2018, NCC-PvPI received seven individual case safety reports (ICSRs) of cefepime associated urticaria. The cases were reviewed by the Signal Review Panel (SRP) at the NCC-PvPI, IPC, and a strong causal relationship between cefepime and urticaria was found. The revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

#### Reference:

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

## Cefotaxime

### Risk of angioedema

**India.** The NCC-PvPI, IPC has advised the CDSCO to revise the PIL for cefotaxime to incorporate angioedema as a clinically significant adverse drug reaction.

Cefotaxime is an antibacterial indicated for the treatment of infections, septicaemia and prophylaxis of surgical infections. Between July 2011 to July 2018, NCC-PvPI received 16 ICSRs of cefotaxime associated angioedema. The cases were reviewed by SRP, PvPI, IPC and

a strong causal relationship between cefotaxime and angioedema was found.

#### Reference:

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

## Cyclin-dependent kinase 4/6 inhibitors

### Rare but severe lung inflammation

**USA.** The US Food and Drug Administration (FDA) has approved of new warnings of rare but severe inflammation of the lungs in the prescribing information and patient package inserts for palbociclib (Ibrance®), ribociclib (Kisqali®) and abemaciclib (Verzenio®).

Cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors are used to treat adults with hormone receptor-positive, human epidermal growth factor 2-negative, advanced or metastatic breast cancer.

Health-care professionals should monitor patients regularly for pulmonary symptoms indicative of interstitial lung disease and pneumonitis. Patients should not stop taking the medicine without talking to a health-care professional.

#### Reference:

Safety Alerts for Human Medical Products, US FDA, 13 September 2019 ([www.fda.gov](http://www.fda.gov))

(See WHO Pharmaceuticals Newsletter No.2, 2019: Risk of interstitial lung disease in Japan)

## Daratumumab

### Risk of reactivation of hepatitis B virus

**1. United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that

the product information for daratumumab will be updated to include the risk of reactivation of hepatitis B virus (HBV).

Daratumumab is indicated for the treatment of adult with newly diagnosed multiple myeloma and relapsed and refractory multiple myeloma.

A recent EU review of worldwide data has identified reports of HBV reactivation in patients treated with daratumumab. There were six cases observed in clinical trials in patients with multiple myeloma.

Previous autologous stem cell transplant and concurrent and/or prior lines of immunosuppressive therapy are risk factors of HBV reactivation.

Health-care professionals should screen all patients for HBV before initiation of daratumumab and monitor patients. Also, they should stop treatment with daratumumab in patients with HBV reactivation and institute appropriate treatment in consultation with experts.

#### Reference:

Drug Safety Update, MHRA, 19 August 2019 ([www.gov.uk/mhra](http://www.gov.uk/mhra))

**2. Ireland.** The Health Products Regulatory Authority (HPRA) has announced that the product information for daratumumab (Darzalex®) has been updated to include a safety warning about the risk of HBV in patients treated with daratumumab.

#### Reference:

Drug Safety Newsletter, HPRA, August 2019 ([www.hpra.ie](http://www.hpra.ie))

## Direct acting oral anticoagulants (DOACs)

### Risk of recurrent thrombotic events

**1. Australia.** The Therapeutic Goods Administration (TGA) has announced that the product information for direct acting oral anticoagulants (DOACs) in Australia is being updated to include information about the increased risk of recurrent thrombotic events in patients diagnosed with antiphospholipid syndrome (APS).

DOACs marketed in Australia are apixaban (Eliquis®), dabigatran etexilate (Pradaxa®) and rivaroxaban (Xarelto®). DOACs are indicated in adults for the prevention of venous thromboembolic events, stroke, systemic embolism, treatment of deep vein thrombosis and pulmonary embolism.

A clinical trial (TRAPS study 1) has shown an increase in the risk of recurrent thrombotic events with rivaroxaban compared to warfarin in patients with APS. While there are currently no completed controlled trials relating to this issue for the other two DOACs in Australia, these medicines may be associated with a similar risk.

Health-care professionals are advised to identify patients who are receiving treatment with a DOAC and review whether continued treatment is appropriate. Patients should be encouraged to discuss any issues or concerns they have about their treatment with a health-care professional.

#### Reference:

Medicines Safety Update, TGA, 26 August 2019 ([www.tga.gov.au](http://www.tga.gov.au))

**2. New Zealand.** Medsafe has announced that an increased

rate of recurrent thrombotic events has been noted in patients with antiphospholipid syndrome (APS) treated with rivaroxaban (Xarelto®) compared to those treated with warfarin.

APS patients included in a recently published study were at high risk of thromboembolic events (triple positive for lupus anticoagulant, anticardiolipin and anti-beta-2 glycoprotein I antibodies). Major bleeding occurred in seven percent of patients in the rivaroxaban group compared to three percent of patients in the warfarin group.

There are no completed similar trials for the other DOACs available in New Zealand (apixaban (Eliquis®) and dabigatran (Pradaxa®)), but since the mechanism of action is similar to rivaroxaban, a precautionary approach is recommended with all DOACs.

#### Reference:

Prescriber Update, Medsafe, September 2019 ([www.medsafe.govt.nz/](http://www.medsafe.govt.nz/))

*(See WHO Pharmaceuticals Newsletter No.4, 2019: Increased risk of recurrent thrombotic events in UK; No.3, 2016: Risk of thrombocytopenia in Japan; No.2, 2016: Benefit-risk balance of rivaroxaban: unchanged in EU; No.6, 2013: Apixaban, dabigatran and rivaroxaban in UK)*

## Dopamine receptor agonists

### Risk of drug withdrawal syndrome

**Japan.** The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for dopamine receptor agonists should be revised to include drug withdrawal symptoms such as apathy, anxiety, depression, fatigue, sweating and pain as adverse drug reactions.

Dopamine receptor agonists are indicated to treat a variety of conditions, for example Parkinson's disease. They include ropinirole (ReQuip®), pramipexole (Mirapex-LA®), talipexole (Domin®), rotigotine (Neupro patch®) and cabergoline (Cabaser®).

Cases of drug withdrawal syndrome have been reported in Japan and overseas. Taking into consideration the potential mechanisms in which dopamine receptor agonists can induce drug withdrawal syndrome, MHLW and PMDA have concluded that the revision of the package inserts was necessary.

#### Reference:

Revision of Precautions, MHLW/PMDA, 22 August 2019 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Febuxostat

### Increased risk of cardiovascular death and all-cause mortality

**Ireland.** The HPRA has announced that the product information for febuxostat will be updated to include the risk of cardiovascular death and all-cause mortality in patients with gout and a history of major cardiovascular disease, following results of a clinical study (the CARES study).

Febuxostat is a non-purine selective inhibitor of xanthine oxidase indicated for the treatment of chronic hyperuricaemia.

The CARES study is a randomised, double-blind trial that recruited patients from USA, Canada and Mexico. The incidence of cardiovascular death was significantly higher in the group that received febuxostat than in the group that received allopurinol. The rate of all-cause mortality was also higher in patients taking febuxostat than in those taking allopurinol.



Patients with pre-existing major cardiovascular disease should not be treated with febuxostat unless no other treatment options are appropriate.

**Reference:**

Drug Safety Newsletter, HPRA, August 2019 ([www.hpra.ie](http://www.hpra.ie))

*(See WHO Pharmaceuticals Newsletter No. 4, 2019: Potential risk of cardiovascular death in Japan; No.2, 2019: Increased risk of death in USA; No.6, 2017: Potential risk of heart-related death in USA; No.3, 2016: Risk of heart failure in Canada)*

## Fingolimod

### Risk of congenital malformations

**Europe.** The European Medicines Agency (EMA) has recommended that fingolimod (Gilenya®) must not be used in pregnant women of child bearing age who are not using effective contraception, due to the risk of birth defects.

Fingolimod is indicated to treat adults and children over 10 years of age with highly active relapsing-remitting multiple sclerosis.

The recommendations follow a review triggered by reports suggesting that the risk of birth defects in infants exposed to fingolimod during pregnancy is twice as high than the estimated risk in the general population, which is 2-3 % according to the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT). Reported major malformations in infants included congenital heart diseases, renal abnormalities and musculoskeletal abnormalities.

Health-care professionals should ensure that female patients of childbearing potential are informed of the risks and that effective contraception is used during treatment and for two months

after treatment discontinuation. If a woman becomes pregnant during treatment, fingolimod must be discontinued.

**Reference:**

EMA, 26 July 2019 ([www.ema.europa.eu](http://www.ema.europa.eu))

## Freeze-dried BCG vaccine

### Risk of meningitis

**Japan.** The MHLW and the PMDA have announced that the package insert for freeze-dried BCG vaccine (Freeze-Dried BCG Vaccine®) should be revised to include meningitis as an adverse drug reaction.

Freeze-dried BCG vaccine is indicated for prophylaxis of tuberculosis.

One case of tuberculous meningitis has been reported in Japan during the previous three fiscal years. A causal relationship between the vaccine and event could not be excluded. No patient mortalities have been reported. MHLW and PMDA have concluded that revision of the package insert was necessary based on the investigation of the currently available evidence.

**Reference:**

Revision of Precautions, MHLW/PMDA, 22 August 2019 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Glibenclamide

### Risk of palpitations

**India.** The NCC-PvPI, IPC has advised CDSCO to request the revision of the PIL for glibenclamide to include palpitations as an adverse drug reaction.

Glibenclamide is used for the treatment of diabetes mellitus. Between July 2011 and

December 2018, NCC-PvPI received 12 ICSRs of glibenclamide associated palpitation. The NCC-PvPI also assessed 103 relevant reports from the WHO global database for reports of adverse events and the literature. A signal was published by the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) which identified this reaction as a signal in the Asian population. The cases were reviewed by SRP at the NCC-PvPI, IPC, and a strong causal relationship between glibenclamide and palpitations was suggested. The revision of the PIL was necessary based on the results of the investigation of the currently available evidence.

**Reference:**

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

*(See WHO Pharmaceuticals Newsletter No. 2, 2019: (Signal) Glibenclamide/glyburide and palpitations in the Asian population)*

## Liposomal medicines

### Name change to avoid medication errors

**Europe.** The EMA has announced that all marketing authorisation holders of medicines containing liposomal drug delivery systems are requested to change the names of these medicines to avoid medication errors.

This name change aims to make a clearer distinction between liposomal and non-liposomal formulations of the same active substance to avoid medication errors. The two formulations may have different biodistribution and release properties, therefore confusion between formulations can occur and pose serious health risks to patients.

Following consultations with the Pharmacovigilance Risk Assessment Committee

(PRAC), the following actions were agreed:

“Liposomal” or “pegylated liposomal” should be added after the invented name and before the strength in the summary of product characteristics of the medicines containing liposomal drug delivery system. Also, the European Directorate for the Quality of Medicines (EDQM) standard term “dispersion”, which includes liposomes in the definition, should be used consistently throughout the product information.

**Reference:**

EMA, 31 July 2019  
([www.ema.europa.eu](http://www.ema.europa.eu))

## Modafinil

### Potential risk of congenital malformations

**Ireland.** The HPRA has announced that the product information for modafinil products (Nuvigil® and Provigil®) will be amended to include the current understanding of the risk of congenital malformations in the offspring of women treated with modafinil during pregnancy.

Modafinil is used for excessive sleepiness associated with narcolepsy.

The HPRA have received reports of major congenital malformations including congenital heart defects, hypospadias and orofacial clefts. A causal relationship with modafinil was considered possible.

Modafinil should not be used during pregnancy and women of childbearing potential must use effective contraception. Health-care professionals should ensure that all female patients of childbearing potential are informed of, and fully understand the potential risk and the necessity of using effective contraception. Other

treatment options should be discussed.

**Reference:**

Drug Safety Newsletter, HPRA, August 2019 ([www.hpra.ie](http://www.hpra.ie))

## Montelukast

### Risk of dysphemia

**Ireland.** The HPRA has announced that existing warnings in the product information for montelukast will be updated to include the risk of neuropsychiatric reactions.

Montelukast is indicated for the prophylaxis and treatment of asthmatic conditions. It is known to be associated with neuropsychiatric reactions including nightmares, insomnia, somnambulism, anxiety, agitation, aggressive behaviour, depression and psychomotor hyperactivity.

The EMA’s PRAC completed a periodic review of cases reporting dysphemia with the use of montelukast, and an association between montelukast and dysphemia as well as other closely related speech disorders cannot be excluded.

Health-care professionals and patients should be alert for the occurrence of neuropsychiatric reactions with montelukast.

**Reference:**

Drug Safety Newsletter, HPRA, August 2019 ([www.hpra.ie](http://www.hpra.ie))

## Naltrexone/bupropion

### Risk of dizziness and somnolence

**United Kingdom.** The MHRA has added a new warning to the product information for naltrexone/bupropion (Mysimba®) indicating the potential risk of dizziness,

somnolence, and rare loss of consciousness or seizure.

Naltrexone/bupropion is indicated for the management of weight in obese and overweight adults.

An EU review of cumulative data has identified somnolence and loss of consciousness with naltrexone/bupropion, which can affect the ability to drive, operate machinery or perform dangerous tasks.

Health-care professionals should advise patients not to drive, operate machinery or perform dangerous activities while taking naltrexone/bupropion until the patient understands how the medicine affects the patient. If the patient experiences adverse events that may impair driving, the patient must not drive. It is against the law to drive if the patient’s ability is impaired by any medicine.

**Reference:**

Drug Safety Update, MHRA, 19 August 2019  
([www.gov.uk/mhra](http://www.gov.uk/mhra))

## Ofloxacin

### Risk of Stevens Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)

**India.** The NCC-PvPI, IPC has advised the CDSCO to request that the PIL for ofloxacin is revised to incorporate SJS/TEN as a clinically significant adverse drug reaction.

Ofloxacin is used for the treatment of bacterial infections of the skin, lungs, prostate, or urinary tract. Between July 2011 to July 2018, the NCC-PvPI received 81 ICSRs reporting SJS/TEN with the use of ofloxacin. The cases were reviewed by SRP at the NCC-PvPI, IPC, and a strong causal relationship between ofloxacin and SJS/TEN was found.



### Reference:

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

## Phenobarbital

### Risk of DRESS syndrome

**India.** The NCC-PvPI, IPC has advised the CDSCO to incorporate drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) as a clinically significant adverse drug reaction into the PIL for phenobarbital.

Phenobarbital is indicated for the treatment of epilepsy. Between July 2011 to December 2018, the NCC-PvPI received 12 ICSRs of phenobarbital induced DRESS syndrome. The cases were reviewed by SRP at the NCC-PvPI, IPC, and a strong causal relationship between phenobarbital and DRESS syndrome was found.

### Reference:

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

## Quetiapine

### Risk of urinary incontinence

**India.** The NCC-PvPI, IPC has recommended that the PIL for quetiapine is updated to include urinary incontinence as a clinically significant adverse drug reaction.

Quetiapine is an antipsychotic medicine used to treat conditions like schizophrenia, depression, maniac episodes and bipolar disorders. Between July 2011 to July 2018, the NCC-PvPI received six ICSRs of quetiapine induced urinary incontinence. All six ICSRs received by NCC-PvPI were carefully discussed in the SRP meeting and the panel found a strong causal relationship

between quetiapine and urinary incontinence.

### Reference:

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

## Romosozumab

### Risk of cardiovascular events

**Japan.** The MHLW and the PMDA have announced that the package insert for romosozumab (Evenity®) should be revised to include the risk of cardiovascular events.

Romosozumab is indicated for osteoporosis in patients with a higher risk of fracture.

The incidence of cardiovascular events tended to be higher in the romosozumab group compared to the alendronate group in a comparative study conducted overseas.

A total of 36 cases of ischaemic heart disease, cerebrovascular disorder, or death of unknown cause with the use of romosozumab have been reported in Japan during the previous three fiscal years. A causal relationship between the drug and event could not be established for any of the cases. Seven patient mortalities have been reported. However, considering the seriousness of the reported events and status of related overseas measures, MHLW and PMDA have concluded that the revision of the package insert is necessary based on the investigation of the currently available evidence.

### Reference:

Revision of Precautions, MHLW/PMDA, 6 September 2019 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Sulfasalazine

### Risk of DRESS syndrome

**India.** The NCC-PvPI, IPC recommends that the PIL for sulfasalazine is revised to include DRESS syndrome as a clinically significant adverse drug reaction.

Sulfasalazine is used for the treatment of inflammatory bowel disease and rheumatoid arthritis. Between July 2011 to July 2018, NCC-PvPI received 40 ICSRs of sulfasalazine associated DRESS syndrome. These ICSRs were reviewed by the panel of experts in the SRP, at the NCC-PvPI, IPC and a strong causal relationship between sulfasalazine and DRESS syndrome was found.

### Reference:

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

(See WHO Pharmaceuticals Newsletter No.3, 2018: DRESS syndrome in Republic of Korea; No. 4, 2017: Risk of Stevens Johnson Syndrome and toxic epidermal necrolysis in India)

## Tofacitinib

### Increased risk of blood clots and death with higher dose

**1. USA.** The US FDA has approved a Boxed Warning informing of an increase in the risk of blood clots and death with the 10 mg twice daily dose of tofacitinib (Xeljanz®).

Tofacitinib is an oral, immunomodulatory disease-modifying anti-rheumatic drug, indicated for the treatment of rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.

When the FDA approved tofacitinib in 2012, it requested a post-marketing clinical trial in patients with rheumatoid arthritis taking methotrexate, to evaluate the risk of heart-related events, cancer and infections. An interim analysis of the trial's results found an increased occurrence of blood

clots and death in patients treated with tofacitinib 10 mg twice daily compared to patients treated with tofacitinib 5 mg twice daily or a tumor necrosis factor (TNF) blocker.

Health-care professionals should discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis. Also, health-care professionals should avoid tofacitinib in patients who may have a higher risk of thrombosis. When treating ulcerative colitis, tofacitinib should be used at the lowest effective dose and the 10 mg twice daily dosage should be limited to the shortest duration needed.

**Reference:**

Safety Alerts for Human Medical Products, US FDA, 26 July 2019 ([www.fda.gov](http://www.fda.gov))

**2. Japan.** The MHLW and the PMDA have announced that the package insert for tofacitinib (Xeljanz®) should be revised to include venous thromboembolism as an adverse drug reaction.

Based on the findings in an ongoing overseas clinical study in patients aged 50 years or older with rheumatoid arthritis and cardiovascular risk factors (A3921133 Study), MHLW and PMDA have considered the necessity of taking measures and concluded that the revision of the package insert was necessary.

Six cases of venous thromboembolism have been reported in Japan during the previous three fiscal years. A causal relationship between the drug and event could not be excluded in these cases. One patient mortality has been reported.

**Reference:**

Revision of Precautions, MHLW/PMDA, 22 August 2019 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

(See WHO Pharmaceuticals Newsletter No.4, 2019: Risk of pulmonary embolism in Europe; No.3, 2019: Increased risk of blood clots in lungs and death in Europe; No.2,

2019: Increased risk of blood clots in the lungs and death in USA)

## Tramadol

### Potential risk of hiccups

**India.** The NCC-PvPI, IPC has made a recommendation requesting that the PIL for tramadol is revised to incorporate hiccups as a potential adverse drug reaction.

Tramadol is used for the treatment of mild to moderate pain. Between July 2011 and December 2018, NCC-PvPI received six ICSRs reporting hiccups associated with the use of tramadol. NCC-PvPI also assessed 83 ICSRs reporting this drug-ADR combination in the WHO global database for reports of adverse events. The cases were reviewed by the SRP-PvPI, IPC, and the information in the cases suggested a strong causal relationship between tramadol and hiccups.

**Reference:**

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

(See WHO Pharmaceuticals Newsletter No.4, 2019: Contraindication in children: Risk of serious respiratory depression in Japan; No.1, 2018: Limited use: Only for adults of 18 years of age and older in USA; No.6, 2017: Contraindication in children and ultra-rapid metabolisers in Australia)

## Tranexamic acid

### Risk of seizure/convulsion

**India.** The NCC-PvPI, IPC has made a recommendation to incorporate seizure/convulsion as a clinically significant adverse drug reaction into the PIL for tranexamic acid marketed in India.

Tranexamic acid is used to prevent or reduce bleeding in certain conditions, such as dental surgery in people with

hereditary blood clotting disorders, cervical surgery, heavy menstrual bleeding, nose bleeds and bleeding inside the eye. Between July 2011 and July 2018, NCC-PvPI received nine ICSRs of seizure/convulsion associated with tranexamic acid use. The ICSRs were carefully reviewed by the expert members of SRP, PvPI and the information in the cases suggested a strong causal relationship between tranexamic acid and seizure/convulsion.

**Reference:**

Based on the communication from NCC-PvPI, IPC India ([ipc.gov.in](http://ipc.gov.in))

## Trelagliptin

### Contraindications removed in patients with renal impairment

**Japan.** The MHLW and the PMDA have announced that the package insert for trelagliptin (Zafatek®) should be revised to remove contraindications in patients with severe renal impairment.

Trelagliptin is indicated for type 2 diabetes mellitus.

When trelagliptin was authorized in Japan in 2015, a clinical pharmacology study was conducted. The study indicated higher plasma concentrations in patients with severe renal impairment and end stage renal failure, compared to patients with normal renal function. Based on this, trelagliptin was contraindicated in patients with severe renal impairment and end stage renal failure.

Later, the marketing authorization holder conducted a clinical study to examine the efficacy and safety of trelagliptin. PMDA concluded that the safety profile of trelagliptin used in patients with severe renal impairment and end stage renal failure is acceptable if administered once

weekly. There were no clinically significant problems in the safety profile of these patients compared to patients with normal renal functions and with mild to moderate renal impairment in the clinical study.

Patients with impaired renal function should be monitored when trelagliptin is administered.

**Reference:**

Revision of Precautions,  
MHLW/PMDA, 6 September  
2019 ([www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## ***Artemisia annua***

### **Risk of QT interval prolongation**

**New Zealand.** Medsafe has announced that patients taking natural health products containing *Artemisia annua* may be at risk of QT interval prolongation.

*Artemisia annua*, (also known as *Qing hao*, Sweet Annie or Sweet Wormwood) dried herb or extract are constituents in several natural health products available in New Zealand. Artemisinin is a constituent of *Artemisia annua* and its derivatives form artemisinin-based combination therapies for treating malaria. New Zealand does not have a register of herbal medicines or an approval system for natural health products.

Health-care professionals should advise patients at risk of QT prolongation to carefully check the ingredients of natural health products and dietary supplements before use. Patients taking medicines that can cause QT-prolongation or patients who are at risk of QT interval prolongation should avoid taking products containing *Artemisia annua*.

#### **Reference:**

Prescriber Update, Medsafe, September 2019 ([www.medsafe.govt.nz/](http://www.medsafe.govt.nz/))

## **Carfilzomib**

### **Risk of cardiac events**

**United Kingdom.** The MHRA has announced that cases of cardiac arrest, cardiac failure and myocardial infarction were reported in patients taking carfilzomib (Kyprolis®).

Carfilzomib is indicated to treat adult patients with multiple myeloma.

Five cases of cardiac failure, five of arrhythmia, three of

cardiac arrest, two of pericarditis, two of left ventricular failure and five of myocardial infarction, of which six were fatal, have been reported in the UK since 2013 to July 2019 in post-marketing reports and in clinical trials.

The risk of cardiac failure with carfilzomib is increased in elderly and in Asian patients. Although adequate hydration is required before starting treatment, all patients should be monitored for evidence of volume overload.

Health-care professionals should monitor patients for signs and symptoms of cardiac disorders and stop carfilzomib if severe cardiac events occur. Restarting treatment may be considered at a lower dose once the condition is controlled.

#### **Reference:**

Drug Safety Update, MHRA, 19 August 2019 ([www.gov.uk/mhra](http://www.gov.uk/mhra))

## **Hepatitis C medicines**

### **Rare occurrence of serious liver injury**

**USA.** The US FDA has announced that it has received cases of worsening liver function or liver failure in patients taking hepatitis C medicines (Mavyret®, Zepatier® and Vosevi®).

Health-care professionals should continue to prescribe the medicines as indicated in the prescribing information for patients without liver impairment or with mild liver impairment. Also, they should assess severity of liver disease at baseline and closely monitor for signs and symptoms of worsening liver function such as an increase in liver enzymes, jaundice, ascites, encephalopathy and variceal hemorrhage. The medicines should be discontinued in

patients who develop signs and symptoms of liver decompensation.

#### **Reference:**

Safety Alerts for Human Medical Products, US FDA, 28 August 2019 ([www.fda.gov](http://www.fda.gov))

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of hepatic impairment and jaundice in Japan)

## **Ingenol mebutate**

### **Potential risk of skin cancer**

**Europe.** The EMA has announced that PRAC has started a review of data on skin cancer in patients using ingenol mebutate (Picato®).

Ingenol mebutate is indicated to treat actinic keratosis, a skin condition caused by overexposure to sunlight.

The PRAC will review all available data (including ongoing studies), assess the impact of the data on the benefit-harm balance of ingenol mebutate use and recommend whether the medicine's marketing authorisation in the EU should be amended.

Health-care professionals should use ingenol mebutate with caution in patients that have had skin cancer in the past. Patients should continue to watch for any skin lesions and inform their health-care professionals immediately if they notice anything unusual.

#### **Reference:**

EMA, 6 September 2019 ([www.ema.europa.eu](http://www.ema.europa.eu))

(See WHO Pharmaceuticals Newsletter No.3, 2017: Risk of hypersensitivity reactions, herpes zoster and eye injury in Australia; No.5, 2015: Risk of severe allergic reactions and herpes zoster (shingles) in the USA)

## **Lamotrigine**

### **Risk of haemophagocytic**

## lymphohistiocytosis (HLH)

**New Zealand.** Medsafe has announced that haemophagocytic lymphohistiocytosis (HLH) has been reported internationally in patients taking lamotrigine.

Lamotrigine is indicated to treat epilepsy and bipolar disorder. HLH is a very serious, possibly life-threatening reaction arising from excessive activation of the body's immune system.

Up to June 2019, the Centre for Adverse Reactions Monitoring (CARM) had not received any reports of HLH associated with lamotrigine use, but if HLH is suspected, lamotrigine should be discontinued.

### Reference:

Prescriber Update, Medsafe, September 2019 ([www.medsafe.govt.nz/](http://www.medsafe.govt.nz/))

(See WHO Pharmaceuticals Newsletter No.6, 2018: Risk of haemophagocytic syndrome in Japan; No.3, 2018: Serious immune system reaction in USA)

## Methimazole

### Risk of inflammation of pancreas

**Canada.** Health Canada has announced that there is a link between methimazole (Tapazole®) and the risk of acute pancreatitis.

Methimazole, also known as thiamazole, is a prescription drug to treat hyperthyroidism, a condition where too much thyroid hormone is produced.

Health Canada reviewed the potential risk of inflammation of the pancreas with the use of methimazole after being made aware of international reports. At the time of the review, Health Canada received 21 Canadian reports of potential acute pancreatitis related to methimazole use.

Health Canada's review of available evidence concluded

that there is a link between methimazole and the risk of acute pancreatitis. Health Canada is working with the manufacturers to update the safety information for methimazole products to inform health-care professionals and patients about this risk.

### Reference:

Summary Safety Review, Health Canada, 12 September 2019 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

(See WHO Pharmaceuticals Newsletter No.2, 2019: Risk of acute pancreatitis in UK)

## Paracetamol

### Dangerous when not used correctly

**New Zealand.** Medsafe has announced that they have received cases of serious adverse events related to medication errors associated with prescribing, dispensing and communication to caregivers in children.

Paracetamol, also known as acetaminophen, is generally indicated to treat mild to moderate pain relief.

The Medicines Adverse Reactions Committee (MARC) discussed a report of acute hepatic failure in a child given a suspected paracetamol overdose.

Following a review of the cases, advice on actions to take when prescribing and dispensing paracetamol for children were provided. For example, paracetamol should be used only for approved indications (pain, fever). The correct dose should be calculated using body weight. Health-care professionals should prescribe paracetamol precisely and dispense diligently.

### Reference:

Prescriber Update, Medsafe, September 2019 ([www.medsafe.govt.nz/](http://www.medsafe.govt.nz/))

(See WHO Pharmaceuticals Newsletter No.2, 2019: Unpredictable pharmacokinetics in overdose in New Zealand; No.1, 2018: Suspension in EU market: due to difficulty in managing overdose in EU; No.5, 2017: Modified- or prolonged-release)

## Tocilizumab

### Rare risk of hepatic injury

**Ireland.** The HPRA has announced that serious cases of drug-induced liver injury, (such as acute liver failure, hepatitis and jaundice and cases requiring liver transplantation) have been observed in patients treated with tocilizumab (RoActemra®).

Tocilizumab is an interleukin inhibitor indicated for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis and chimeric antigen receptor T-cell-induced severe cytokine release syndrome.

A recent review of data from clinical trials, non-interventional studies, spontaneous reports, and the published literature identified eight cases of tocilizumab-related drug-induced liver injury worldwide. Two cases of acute liver failure required liver transplantation.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be monitored in patients. Also, patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury. Health-care professionals should refer to the guidance in the approved product information.

### Reference:

Drug Safety Newsletter, HPRA, August 2019 ([www.hpra.ie](http://www.hpra.ie))

(See WHO Pharmaceuticals Newsletter No.4, 2019: Risk of hepatotoxicity in Australia and UK)

## Tramadol

### Possible risk of opioid effects in breastfed babies

**New Zealand.** Medsafe has announced that CARM received a case report where a neonate suffered feeding disorder, somnolence (sleepiness), respiratory disorder and weight decrease while the breastfeeding mother was taking tramadol (Tramal® and Arrow®).

Tramadol is indicated for the relief of moderate to severe pain and is used to help manage pain after a caesarean section.

Small amounts of tramadol and its metabolite, which also helps with pain, are found in breast milk when taken by the mother. Although the amounts of tramadol and its metabolite are too low to cause a problem, there is a risk that the baby's breathing may be affected or that the baby may be allergic to tramadol or its metabolite.

Medsafe will continue to monitor this issue and will produce updated advice for health-care professionals and consumers as necessary.

#### Reference:

Safety Communications,  
Medsafe, 9 August 2019  
([www.medsafe.govt.nz/](http://www.medsafe.govt.nz/))

*(See WHO Pharmaceuticals Newsletter No.4, 2019: Contraindication in children: Risk of serious respiratory depression in Japan; No.1, 2018: Limited use: Only for adults of 18 years of age and older in USA)*

Medsafe encourages health-care professionals to perform liver function tests before starting and stopping treatment. Also, the use of vildagliptin should be avoided during pregnancy unless the expected benefits outweigh any potential risks.

The CARM received 15 reports where vildagliptin was suspected. The 15 reports describe 36 reactions, including hepatic reactions, oedema, cardiac disorders, mood disorders and gastrointestinal disorders.

#### Reference:

Prescriber Update, Medsafe,  
September 2019  
([www.medsafe.govt.nz/](http://www.medsafe.govt.nz/))

## Vildagliptin

### Risk of hepatotoxicity

**New Zealand.** Medsafe has announced that hepatotoxicity is the most significant risk of harm with vildagliptin.

Vildagliptin is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes.



**New measures to avoid valproate exposure in pregnancy**

Valproate-containing medicines (valproate medicines) are used to treat epilepsy and bipolar disorder, and in some countries, they are also used for the prevention of migraines.

Valproate medicines (e.g. sodium valproate, valproic acid, divalproex) are known to increase the risk of birth defects (such as spina bifida, facial, skull, limb and heart malformations) and developmental problems in babies who are exposed to valproate in the womb. Previous data have shown that children exposed to valproate in the womb are also at increased risk of autistic spectrum disorder (around 3 times higher than in the general population) and childhood autism (5 times higher than in the general population). There are also limited data suggesting that children exposed to valproate in the womb may be more likely to develop symptoms of attention deficit hyperactivity disorder (ADHD). Recent studies have also identified developmental problems in up to 30 to 40% of pre-school children exposed to valproate in the womb, including delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability.

Previous regulatory measures, to inform women of the risks of taking valproate have not been very effective; women did not always receive adequate and correct information on valproate in a timely manner. The European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC), has recommended new measures to avoid the use of valproate medicines in pregnancy.

The new measures on valproate medicines include the following:

- Ban on use for migraine or bipolar disorder in pregnancy;
- Ban on use for treating epilepsy during pregnancy unless there is no other effective treatment available;
- Not to be used in women of child bearing age unless they meet the conditions of the new valproate pregnancy prevention programme;
- Change in packaging, to display a visual warning of pregnancy risks (in the form of boxed text with other possible elements such as a warning symbol); the warning must also be included on patient cards attached to the box and supplied with the medicines each time it is dispensed;
- Companies that market valproate medicines should also provide updated educational material in the form of guides to healthcare professionals and patients.

Additionally, the PRAC has recommended that the companies marketing valproate medicines should carry out additional studies to further characterise the nature and extent of the risks posed by valproate, and to monitor ongoing valproate use and the long-term effects from affected pregnancies.

While the above measures were issued for EU member states, the risks with valproate in pregnancy are equally relevant, to all women, in all countries, worldwide. Compliance with these recommended regulatory measures in different jurisdictions outside of Europe is just as important and is encouraged.

Valproate and other medicines with teratogenic issues are often discussed at the meetings of the World Health Organization (WHO) Advisory Committee on Safety of Medicinal Products (ACSoMP). A 'hot topics' list is being developed by WHO, for products such as valproate medicines, to always include discussions on these medicines in the working agenda of the WHO ACSoMP.

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 21 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. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, 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 25). 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, on the UMC Measures of Disproportionate Reporting etc., visit [www.who-umc.org](http://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](mailto:signals@who-umc.org).

## Levonorgestrel-releasing intrauterine system products and suppressed lactation

Marielle Lavalley and Alima Tapsoba, Health Canada

### Summary

In April 2018, a signal detection screening in VigiBase, the WHO global database of individual case safety reports, was designed to detect safety concerns reported by patients. A total of 181 case reports of suppressed lactation in women using Levonorgestrel (LNG)-releasing intrauterine systems (IUS) were identified to require further in-depth review. In 152 cases of these 181 reports, LNG-IUS is the single reported drug product. The reports originated from Australia, Europe, North and South America. Of the 181 reports, 51% were reported by consumers. Positive dechallenge was reported for 17 cases, of which this review will highlight three well documented key cases providing objective evidence of suppressed lactation using LNG-IUS products.

There are currently no literature references suggesting that LNG-IUS products decrease breast milk production in breastfeeding mothers. However, isolated cases of suppressed lactation with the use of LNG-IUS are labelled in the USA and Canada based on post-marketing experience. These reports suggest that health care professionals and patients worldwide may benefit from increased awareness of the occurrence of isolated post-marketing reports of decreased milk production among women using LNG-IUS products.

### Introduction

Levonorgestrel is a second-generation progestin drug. It is widely used for contraception. For pregnancy prevention, levonorgestrel may be used alone or as combined oral contraceptives pills with oestrogen. Levonorgestrel single medicinal ingredient products include: emergency birth control pills; intrauterine devices and birth control implants. In this review, we focus on Levonorgestrel (LNG)-releasing intrauterine system (IUS) products.

LNG-IUSs are polyethylene T-shaped devices that contain LNG. After insertion of the device into the uterus, a low-dose of levonorgestrel is released at a relatively constant rate, which reduces systemic effects.

LNG-IUSs can provide contraception for three or five years, depending on the device. LNG-IUSs are considered long acting reversible contraception (LARC) and are listed among the most effective contraceptive methods because they do not depend on compliance from the user. In addition to their high efficacy, LNG-IUSs are commonly used because of their safety, ease of use, and cost effectiveness.<sup>1,2,3</sup> The LNG-IUS products are available in multiple formulations (52 mg, 19.5 mg and 13.5 mg LNG).

Both the World Health Organization and the Centers for Disease Control and Prevention Medical Eligibility Criteria for Contraceptive use list LNG-IUS

products as category 1 or 2 for postpartum breastfeeding women, which means there are no restrictions (category 1) or that the advantages of using the method generally outweigh the theoretical or proven risks (category 2).<sup>1,4</sup>

Given that a high progesterone level during pregnancy prevents prolactin (PRL) release and onset of lactation, there is a theoretical concern that LNG-IUS used for postpartum contraception may cause an increase in the progesterone level sufficient to inhibit PRL release and therefore suppress/decrease lactation. Investigations have shown that due to individual variations, some women using LNG-IUS may have a systemic hormone distribution which could explain minor hormonal systemic side effects such as acne, hirsutism, headache and mood changes.<sup>5</sup> Although this mechanism could be the most plausible explanation of an eventual systemic effect on PRL inhibition, it has been demonstrated that the LNG-IUS effect is mainly local and plasma LNG concentration from LNG-IUS are lower than with other contraceptive methods i.e. implants, progestin only pills and combined oral contraceptives.<sup>5,6</sup> Therefore, the biological mechanism by which LNG-IUS may cause suppressed lactation remains uncertain.

### Reports in Vigibase

The Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) "Lactation disorder" was highlighted for LNG to be disproportionately reported in Vigibase, the WHO global database of individual case safety reports (ICSRs) during a signal sprint designed to detect safety concerns reported by patients. Following a further evaluation, the search was refined to the MedDRA PT of "suppressed lactation" in Vigibase, on which this signal assessment is based.

A search was performed in Vigibase using the following search parameters:

- Dataset date: 2018-05-02
- Tot. no. ICSRs: 17 122 715
- Terminology: MedDRA 20.1
- Dataset: Full dataset
- Drugs: Levonorgestrel (Substance)
- Reactions: Suppressed lactation (PT)

A total of 218 ICSRs matched this search from which 37 reports were excluded. The rationale for their exclusion was that routes of administration did not meet the criteria of IUS such as per oral, transmammary (parent- child cases), as well as subcutaneous, generating the remaining 181 reports with the MedDRA PT "Suppressed lactation" reported for LNG-IUS products. These reports originated from Australia, Europe, North and South America and concerned women between the ages of 16 to 44 (age unknown in 58 cases). With respect to the source of information, health care professional, consumer, and lawyer was noted as

respectively 61 cases, 93 and one. The reporter was unknown in 26 cases.

In 152 of these 181 reports, LNG-IUS is the single reported drug. In the remaining 29 reports where patients used LNG-IUS with concomitant medications, levonorgestrel was the only suspected drug in 28 reports. Most of the concomitant medications reported are prenatal/multivitamins, iron, calcium, pain killers such as naproxen or ibuprofen, natural health products such as chlorophyll, fish oil etc. Three reports had drugs used to stimulate milk production (galactagogues) such as domperidone (one case) or fenugreek. Two cases had combined oral contraceptives (ethinylestradiol/ norethisterone and ethinylestradiol/norgestimate) reported as concomitant with the IUS. One report included lamotrigine. For 94 of these 181 reports, suppressed lactation was the only reaction reported. The time-to-onset varied from 0 days to 2 months and was not specified in 141 cases. 73 reports were reported as serious according to ICH seriousness criteria.

Several physiological factors can cause decreased/suppressed lactation (stress, infrequent breastfeeding, introduction of formula, etc.). Information regarding possible maternal or neonatal factors is not available in the reports. Information on objective evidence suggesting decreased lactation (such as infant weight, stool/urine outputs, amount of breast milk expressed before and after insertion of the IUS etc.) is missing in most of these reports.

Positive dechallenge (Drug withdrawn/Reaction abated) was reported for 17 cases, of which seven were identified from narratives in Canadian reports. The following three cases describe an established lactation prior to the insertion of the IUS and the reporter provided objective evidence which may imply decreased lactation (e.g. effect on infant weight or decrease in breast milk expressed). From the reported medical history and concomitant medicines, the reported event "suppressed lactation" is unlikely to be attributable to disease or other concomitant drugs. In addition, there was a positive dechallenge (only treatment was removal of the IUS and milk supply returned back to normal) and recovery outcome implies sustained resumption of effective lactation and breastfeeding after IUS removed.

**Case 1:** A physician described the patient experience with LNG-releasing intrauterine device (IUD) as "Mother has Mirena IUD inserted. Baby did not gain weight. The change from a baby who was previously gaining weight very well was chronologically related to the IUD. Removal of IUD"

**Case 2:** Similarly, another Lactation doctor reported the following regarding the patient "Patient had Mirena inserted about 6 months postpartum and was pumping her breast. At the time of insertion she was pumping 4-5x/day and

getting 60-80 ml per breast. Her supply gradually decreased to 20-30 per breast and the letdown would take 8-10 minutes. IUD removed and supply was back within 1 week, Also the letdown now very fast".

**Case 3:** A family physician detailed patient experiences while on LNG as follows "Patient had Mirena IUD for contraception at the time of breast feeding. Milk supply dropped within 7-10 days. IUD was removed and ten days after removed, her milk supply returned back to normal."

### Literature and Labelling

Health Canada reviewed the risk of decreased breast milk production with the use of LNG-IUS products (Mirena, Jaydess, and Kyleena) because of 19 Canadian reports in breastfeeding women using Mirena. Health Canada's safety review took into consideration scientific and medical literature, Canadian and international adverse reaction reports, as well as known information about the use of LNG-IUS products in Canada and internationally. During the assessment, Health Canada reviewed 24 published studies about women who were breastfeeding and using LNG-IUS products (scientific literature search from 1974 to February 2017). These studies concluded that the use of LNG-IUS provides highly effective birth control and that these products do not affect breastfeeding.<sup>7</sup> An additional search covering the period from 2017 to 2018 in Embase, Medline, CAB Abstracts, Global Health and IPA did not provide any evidence suggesting that LNG-IUS products decreased breast milk production in breastfeeding mothers. This shorter period was chosen since this search for the period from 1974 to Feb 2017 had already been performed by Health Canada previously.

Health Canada's review concluded there is limited evidence to suggest a link between levonorgestrel intrauterine devices and the risk of decreased breast milk production due to a lack of published literature and a biological mechanism that is not clear. However, there are Canadian reports of suppressed lactation in breastfeeding women using LNG-IUS with a probable/ possible causality.<sup>7</sup> As a result of the national assessment, Health Canada updated the product information of LNG-IUS products and the current Canadian labelling states that isolated post-marketing cases of decreased milk production have been reported in women using a LNG-IUS.<sup>8,9,10</sup>

The US Food and Drug Administration's (FDA's) labelling<sup>11,12,13</sup> for LNG-IUS products states that isolated cases of decreased milk production have been reported with a LNG-releasing IUS. However, post-marketing cases of decreased or suppressed lactation with the use of LNG-IUS is not labelled in other parts of the world.<sup>14-17</sup> The labelling of these products reads "A levonorgestrel-releasing intrauterine system does not affect the quantity or quality of breast milk".<sup>16</sup>

### Conclusion

There are currently no literature references suggesting that LNG-IUS products decrease breast milk production in breastfeeding mothers and the biological plausibility of suppressed lactation remains unclear. However, there are post-market reports of suppressed lactation in breastfeeding women using LNG-IUS with a probable/ possible causality. Isolated cases of suppressed lactation with the use of LNG-IUS is labelled in the USA and Canada based on post-marketing experience. This risk should be labelled consistently for all LNG-IUS products worldwide so that health care professionals and patients may benefit from increased awareness of the occurrence of isolated post-marketing reports of decreased milk production among women using LNG-IUS products.

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## Vortioxetine and aggression

Corine Ekhart and Dr. Florence van Hunsel, the Netherlands Pharmacovigilance Centre Lareb and Rebecca E. Chandler, Uppsala Monitoring Centre

### Summary

Vortioxetine is a new chemical entity licensed for the indication of major depressive disorder. With a complex pharmacological mechanism of action, it modulates neurotransmission within the serotonin system, as do serotonin reuptake inhibitors, but also within a number of other systems which are thought to account for additional effects such as

improved cognition. A statistical screening of VigiBase, the WHO global database of individual case safety reports, performed in April 2018 and designed to detect safety concerns reported by patients, highlighted the combination vortioxetine and aggression. Given the multimodal actions of vortioxetine, the strength of the clinical support from the case series, and the evidence for a potential role of serotonin in aggression, there is

adequate support for a potential causal relationship between vortioxetine and aggression. Current product information for vortioxetine does not sufficiently inform patients about the potential of aggression as an adverse effect.

## Introduction

Vortioxetine (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine), a structurally new type of psychotropic medication, is considered to have a multimodal pharmacological mechanism of action. In vitro studies have revealed it to be 5-HT<sub>3</sub>, 5-HT<sub>7</sub>, and 5-HT<sub>1D</sub> receptor antagonist, a 5-HT<sub>1B</sub> receptor partial agonist, a 5-HT<sub>1A</sub> receptor agonist, and an inhibitor of the 5-HT transporter. Animal models suggest that it modulates neurotransmission within several systems, predominantly the serotonin but probably also the norepinephrine, dopamine (DA), histamine, acetylcholine, GABA and glutamate systems. This multi-modal activity is thought to be responsible for the differences between vortioxetine and the class of serotonin reuptake inhibitors (SSRIs) with vortioxetine exhibiting additional effects such as increased synaptic plasticity and improved cognitive function.<sup>1</sup>

Vortioxetine was approved for use in the treatment of major depressive disorder in adults in the United States of America (USA) and the European Union (EU) in 2013.

At the time of licensure by the European Medicines Agency (EMA), vortioxetine received a black triangle warning, and the risk management plan included a post-authorisation safety study with an aim to "... further characterise the safety profile of vortioxetine by assessing the frequency of the certain events related to important potential risks in patients treated with vortioxetine."<sup>2</sup>

Aggression is defined as "forceful physical, verbal, or symbolic action which may be appropriate and

self-protective or inappropriate; aggression may be directed toward the environment, another person/personality, or toward the self" in the McGraw-Hill Concise Dictionary of Modern Medicine.<sup>3</sup> Aggression can be a symptom of certain psychiatric disorders, and it may complicate non-psychiatric illnesses when patients feel unrecognised or disregarded by the medical system.<sup>4</sup> Within clinical practice there exist a number of related words which are used interchangeably with "aggression", such as "anger", "hostility", or "irritability". The granularity of this medical concept is reflected in the MedDRA dictionary by the existence of a standardized MedDRA query (SMQ) "Hostility/Aggression".

The biological mechanism behind aggression is complex, involving several cortical and subcortical brain networks which are modulated by number of neurotransmitter systems, including monoamines, glutamate, and GABA, and by ion channels.<sup>5,6</sup> The main receptors and enzymes involved in the neurobiology of aggression include serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors, 5-HT transporters, DA D<sub>1</sub> and D<sub>2</sub> receptors, DA transporters, 1- and 2-adrenoceptors, the enzyme monoamine oxidase (MAO)-A, the GABA system (GABA<sub>A</sub> and GABA<sub>B</sub> receptors and GABA transaminase), the glutamate NMDA and AMPA receptors, and voltage-gated Na<sup>+</sup> and Ca<sup>2+</sup> channels. A clinical manifestation of aggression can occur as a result of dysfunction at genomic and transcriptional levels, as well as at the level of the synthesis and the metabolism of these various neurotransmitters and their receptors.<sup>7,8</sup>

## Reports in Vigibase

Table 1 illustrates the disproportionality of vortioxetine and aggression, as of 30 September 2018.

**Table 1. Vigilyze disproportionality value (dataset date: 2018-09-30)**

Substance	Reaction (PT)	N <sub>observed</sub>	N <sub>expected</sub>	IC <sub>025</sub>	IC	N <sub>country</sub>	N <sub>subst</sub>	N <sub>reaction</sub>
Vortioxetine	Aggression	77	21.52	1.48	1.82	19	8.790	44.299

Based on the overall reporting of adverse reactions for vortioxetine and aggression in Vigibase, the WHO global database of individual case safety reports (ICSRs), the expected value for the number of reports on the combination was 22, while the observed number of reports was 77. The statistical significance of the association is shown by the IC<sub>025</sub> of 1.48.

## The case series

Seventy-six ICSRs reporting the MedDRA preferred term (PT) "aggression" with the use of vortioxetine had been received into Vigibase by 30 August 2018

and were included in this case series review. These reports concerned 45 women, 28 men, with three unknown. Age varied from 15 to 90 years, with a median of 47; age was not provided in 26 reports. The largest number of reports for which age was known was the age group 18-44 years. Reports were primarily received from consumers/non-health professionals (n=41) and physicians (n=23). Reports originated from all continents, including the Americas (USA, Canada), Europe (Austria, Denmark, Czech Republic, the Netherlands, Germany, Finland, Italy, Sweden, France, Norway, Spain, Switzerland, the United Kingdom), Asia (Turkey, Republic of Korea) and Africa (Namibia and South Africa). Twenty-seven of the cases were



reported as “serious” and eighteen reports mention aggression as the only preferred term. The most commonly co-reported adverse drug reactions (ADRs) were irritability (14 reports), suicidal ideation (12 reports) and anger (11 reports).

In 12 reports, time-to-onset was reported. Time-to-onset varied from 0 days to 4 months, with a median of 11 days. Fifteen reports mention that the drug was withdrawn, and the patient recovered (positive de-challenge), while only six reports that the drug withdrawn and there was no effect observed (negative de-challenge). None of the reports mention a positive re-challenge. In 42 reports, vortioxetine was the only suspect drug and no concomitant medication was reported. In 29 reports, vortioxetine was the only suspect drug but there was concomitant medication. In five reports there were drugs reported as “suspect”: escitalopram (two reports), mirtazapine (one report), ondansetron (one report), and clonazepam/lamotrigine/lurasidone/venlafaxine (one report). Aggression is not a known side effect of ondansetron; however agitation is. One report also had clonazepam, lamotrigine, lurasidone and venlafaxine as suspect drugs. Aggression is a known ADR for escitalopram, mirtazapine, clonazepam, lamotrigine and venlafaxine, while agitation is a known ADR for ondansetron and lurasidone.

## Illustrative case reports

### Case 1

A 75-year-old female with severe depression was treated with vortioxetine after she experienced lack of effect with escitalopram. Within weeks of starting treatment, the patient was hospitalized due to aggressive behaviour, confused state, a cramp-like incident in her arms, a strange feeling of heavy arms, and a strange feeling in the body.

The patient had never before shown aggressive behaviour, but while on treatment with vortioxetine, severe aggression developed. The patient slammed wet dishcloths on the table, threw a box with shoes on the floor, banged on the walls and on the toilet door while her spouse was in the toilet. The patient was out of her mind, and the spouse described that the patient was completely out of balance, which he had never observed before.

Vortioxetine was discontinued 24 days after its initiation. Symptoms resolved while hospitalised.

### Case 2

A 42-year-old male with acute depression, he had been treated previously with sertraline but discontinued it due to sexual side effects. The treatment with vortioxetine was initiated at 10 mg. The patient complained that he was irritable on the medication. The dose was increased to 15 mg, after which it was noted that he felt that he became more

aggressive, which was not in his character. He described that he “almost came into conflict with people on a few occasions that could have led to an actual altercation”. He himself stopped the medication. The patient considered other factors for the aggression (work, stress) but felt that vortioxetine was responsible for the change. At the time of this report, he had stopped the medication four days previously and was waiting to see if there was a difference.

### Case 3

A 50-year-old female was treated for major depression with vortioxetine. The patient noted that after the start of the medication, she felt agitated, with motoric unrest. After increasing the dosage from 10 mg to 15 mg, the patient was aggressive and more agitated. The vortioxetine dose was subsequently decreased stepwise from 15 mg to 10 mg to 5 mg, and finally withdrawn. The patient recovered from the agitation/aggression within a week of the withdrawal. Concomitant medication was not reported. The patient had no known medical history, nor known past drug therapy.

### Case 4

A 40-year-old male was started on vortioxetine for major depression. In the second week of therapy, the patient developed severe nausea and diarrhoea as well as a gradual onset of irritability and angry mood. During the third week the patient suffered from strong itching of the lower limbs at night in addition to continued nausea and diarrhoea and a headache every day starting in the morning. The patient reported his condition to his psychiatrist, but was told that these were usual adverse reactions. At the end of fourth week the patient experienced an attack of aggression which “resulted in the destruction of things”. The patient visited the psychiatrist again, no hospitalization was needed, and his medication was immediately changed to Zoloft 100 mg.

## Literature and Labelling

The EU product labelling intended for health care providers (the Summary of Product Characteristics in the EU) only warns that aggression has been observed in paediatric patients being treated with other antidepressants, without a specific mention of vortioxetine.<sup>9</sup> The labelling intended for patients (the Patient Information Leaflet) contains no mention of aggression or other similar terms.<sup>10</sup>

The US Package Insert (intended for both health care providers and patients) refers to the association of aggression with other antidepressants, but it also mentions an aggression-like term (sudden outbursts of anger) in specific association with discontinuation of vortioxetine.<sup>11</sup>

## Discussion and Conclusion

Disproportionality analysis (IC analysis)<sup>12</sup> has revealed a statistically significant increased number of observed cases of aggression with vortioxetine compared to what is expected within the database. Exploration of Vigibase reveals a similarly significant increase in disproportionality for a number of related PT terms, including hostility, violence-related symptom, irritability, verbal abuse.

Review of the cases included in the drug-ADR combination has focused on the specific MedDRA PT "aggression" given the number of cases within the case series with sufficient and rich detail, enabling causality assessment. It is likely that additional clinically relevant cases could be identified by expansion of the case search using the High Level Term Behaviour and Socialisation Disturbances or the SMQ Hostility/Aggression.

Supporting evidence for possible causality from the case series are the wide geographic distribution of cases, a lack of evidence that aggression was part of a larger clinical syndrome in 26 cases, vortioxetine as the only reported drug in 42 reports (and the only suspected drug in 29 additional reports with concomitant medication), and the documentation of a positive de-challenge in 15 cases. A potential confounder in all cases is that of indication for treatment; however, aggression is not usually considered to be related to major depressive disorder which is the only indication for which vortioxetine is licensed. Cases 1 to 4 above were chosen to highlight a number of details which support the causality hypothesis: the clear onset of symptoms (noted to be out of character for these patients) after the initiation of therapy; the lack of apparent confounders, such as concomitant medications; dose-response relationship in two cases; and resolution of symptoms with discontinuation in three cases. Furthermore, three of the cases suggest a clinical pattern in which feelings of agitation/irritability precede the overt manifestation of aggression.

To explore the biological plausibility of a causal association between vortioxetine and aggression the relationship between serotonin and aggression has been reviewed. Serotonin is thought to have a role in the inhibition of impulses and the regulation of emotions and social functioning, which are domains linked to aggression.<sup>13,14</sup> Manchial et al. recount that 5-HT receptors have been investigated in preclinical and clinical studies for their role in mental diseases but also specifically in aggressive behaviour. Involvement of 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors in aggression has been confirmed by pharmacological studies indicating that 5-HT<sub>1A</sub> agonists and partial agonists and mixed 5-HT<sub>1A</sub>/5-HT<sub>1B</sub> partial agonists have potent anti-aggressive properties in animal paradigms of aggressive behaviour. Since vortioxetine is a 5-HT<sub>1B</sub> receptor partial agonist, anti-aggressive behaviour could

possibly be expected. However, they stated that current knowledge does not yet clearly disentangle whether 5-HT dysfunction, most often a 5-HT deficiency, is the cause or the consequence of the aggressive/violent behaviour, of the underlying mental disease(s), or the expression of the comorbidity. Future studies are recommended to clarify the association between changes in 5-HT levels, altered activity of 5-HT receptors and their intracellular signalling cascades, and modifications of 5-HT genes, and in particular, the neurobiological link between the altered 5-HT machinery and aggressive behaviour in the context or in the absence of mental illness.<sup>15</sup>

A causal link between aggression and an analogous class of antidepressants, the SSRIs, has been explored in a number of published articles; however, there is a lack of consensus in the conclusions on causality. An article from Walsh and Dinan reviewed all published papers on Medline and other databases linking serotonin, SSRIs and aggression. They conclude that there is no convincing evidence to link SSRIs causally to violence and suicide. A small proportion of patients treated with SSRIs may become akathisia and others may show increases in anxiety in the initial phase of treatment, but no increased susceptibility to aggression nor suicidality can be connected with the SSRIs. In fact, SSRI treatment may reduce aggression, probably due to positive effects on the serotonergic dysfunction that is implicated in aggressive behaviour directed towards oneself or others.<sup>16</sup> In contrast, the review and analysis by Breggin states that evidence from many sources (clinical reports, controlled clinical trials and epidemiological studies) confirms that SSRIs commonly cause or exacerbate a wide range of abnormal mental and behavioural conditions. This can result in suicidality, violence and other forms of extreme abnormal behaviour. These include the production of feelings that often begin with lesser degrees of insomnia, nervousness, anxiety, hyperactivity and irritability and then progress toward more severe agitation, aggression, and varying degrees of mania. Another proposed mechanism is the production of a combined state of stimulation and depression (an agitated depression) with a high risk of suicide and violence. Additionally, SSRIs can be associated with the production of obsessive preoccupations and/or the production of akathisia, an inner agitation, both of which can lead to aggression against self or others.<sup>17</sup> In spite of the lack of consensus on causality, the Pharmacovigilance Risk Assessment Committee at the EMA concluded that the evidence was enough to include aggression in the product labelling for paroxetine in 2015.<sup>18</sup>

Review of regulatory documentation for vortioxetine has revealed that in pre-clinical studies performed to support the application for licensure, administration of the drug was associated with CNS-related clinical signs in mice, rats and dogs. These included salivation (rat and

dog), pupil dilatation (dog), and convulsions (dogs). Analysis of a subgroup of the clinical trial population ("the MDD short-term pool") revealed an increased proportion of the CNS events of dizziness, abnormal dreams and increased appetite in participants who received vortioxetine. However, the incidence of treatment-emergent adverse events within the SMQ Hostility/Aggression were found to be similar between the placebo group (2.8%) and the vortioxetine total group (1.9%).<sup>2</sup>

Pharmacokinetic data show that several CYP isoenzymes are involved in the metabolism of vortioxetine: CYP2D6, CYP2C9, CYP3A4/5, CYP2A6, CYP2C8, CYP2C19 and CYP2B6. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers (PM) of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers (EM). According to the manufacturer, the approximately two- fold higher vortioxetine exposure in CYP2D6 PMs does not translate into significant changes in the safety and tolerability profile of vortioxetine relative to that in CYP2D6 EMs. However, the frequency of some adverse effects is doubled in the PM group versus the EM group, such as dizziness and pruritus.<sup>2</sup> A small study of 18 patients performed in the Netherlands found no evidence for a significant relationship between CYP2C19 and CYP2D6 polymorphisms and aggression in patients using SSRIs.<sup>19</sup> An expansion of this study using a larger cohort of patients to investigate the relationship between vortioxetine and aggression could be considered.

Given the complexity of the multi-modal actions of vortioxetine and the uncertainties surrounding the role of serotonin in aggression and the strength of the clinical support from the case series, there is adequate evidence to suggest a potential causal relationship between vortioxetine and aggression. The combination of pharmacokinetic data and the two cases suggesting the possibility of a dose response relationship could be used to hypothesize that patients who are CYP2D6 poor metabolizers are at an increased risk for aggression and other ADRs from vortioxetine. Current product information for vortioxetine does not sufficiently inform patients about the potential association with aggression, and the product labelling may need to be revised.

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# CAVEAT DOCUMENT

## **Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).**

*Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.*

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 Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

### **Tentative and variable nature of the data**

*Uncertainty:* 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 is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

*Variability of source:* Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

*Contingent influences:* 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 adverse effects and other factors.

*No prevalence data:* No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

*Time to VigiBase:* Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

**For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.**

**Prohibited 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 VigiBase must include a statement:**

- (i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information
- (ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases
- (iii) affirming that the information does not represent the opinion of the UMC or 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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## Recommendations from the 16th meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

*The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003, to provide advice to WHO, including its Collaborating Centre for International Drug Monitoring (the UMC), and through it, to the Member States of WHO, on safety issues relating to medicinal products. A summary of discussions and key recommendations from the 16th meeting of ACSoMP is provided below.*

### WHO Programme for International Drug Monitoring: A milestone

In November 2018, the WHO Safety & Vigilance (SAV) Team organized a celebration to mark the 50th anniversary of the WHO Programme for International Drug Monitoring (PIDM). The celebratory event was followed by the usual annual (technical) meeting of WHO PIDM members, attended by representatives of national pharmacovigilance centres.

### Collaborations in WHO on Safety & Vigilance

ACSoMP noted that relations continue to get stronger between the WHO SAV team and WHO disease control and treatment programmes. When requested, SAV extracts and reviews data from the WHO global database of Individual Case Safety Reports, Vigibase, on medicines used within these programmes. And through ACSoMP, SAV has been supporting the programmes with timely advice on the safety of these medicines.

ACSoMP members commented that the potential value of greater collaboration with the immunization and vaccines safety programmes would be worth exploring.

**The Council for International Organizations of Medical Sciences (CIOMS)** has the status of a non-State Actor (NSA) in official relations with WHO. SAV team collaborates with CIOMS in preparing the workplan on projects of mutual interest. The workplan for the years 2019-2021 was approved by the Executive Board at its 144<sup>th</sup> Session in January 2019, with a decision to maintain the CIOMS official relations with WHO. The Executive Board will review the status of the implementation of the workplan in 2022, according to its triennial schedule for reviews.

A WHO policy brief, drafted by the **WHO Technology, Standards and Norms (TSN)** Team aims to guide regulators in traceability standards and ensure appropriate governance. Many traceability standards already exist, and WHO does not aim to develop new standards, but to explain the opportunities of track & trace technologies (and their risks), to ensure greater accountability, and to enhance information-sharing. Pharmacovigilance is in scope of the project and the goal for the policy guidance would be to enable local and global pharmacovigilance.

**The Identification of Medicinal Product (IDMP)** standards were developed by the International Organisation for Standardisation (ISO) to facilitate the reliable and consistent exchange of medicinal product information by providing a common product "language". In terms of pharmacovigilance, IDMP standards would enable adverse event reports to be based on a harmonized set of product definitions, improving the quality of data used for signal management, and speeding up communication, decision-making and actions.

WHO SAV and the WHO Regulatory System Strengthening (RSS) teams are organizing a workshop to discuss the IDMP use-cases as well as the maintenance of the Pharmaceutical Product Identifiers (PhPIDs) within the IDMP. ACSoMP welcomed the idea of a global system of identification of medicinal products as this would facilitate pharmacovigilance. A WHO-led joint maintenance strategy for IDMP pharmaceutical product identifiers would be ideal.

**ICH E19 Working Group:** WHO SAV also participates, as an observer in this working group, for the elaboration of the ICH guideline on **Optimisation of Safety Data Collection**. The draft guideline is currently undergoing public consultation, for review and comments.



## WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC)

The Uppsala Monitoring Centre (UMC) has been responsible for the technical and operational aspects of the WHO Programme for International Drug Monitoring since 1978. UMC submitted its current workplan to ACSoMP, listing strategic objectives and activities for 2019. Strategic objectives included: (1) building capacity for pharmacovigilance with a focus on analysis (through in-depth analysis and research, and a range of training methods); (2) identifying who is at risk, why and when (through identifying plausible risks and enabling therapeutic decision-making); (3) focusing on patient perspectives; (4) safeguarding and promoting the clinical value and relevance of information in VigiBase (through new data fields that aid analysis, and by promoting the value of global pharmacovigilance data); and (5) providing a high-quality WHO drug portfolio to support safety management throughout a product's life cycle.

ACSoMP noted that sound methods and tools are needed for risk-benefit assessment and better decision-support. A proposal was made to establish a partner strategy to encourage active and productive collaboration between WHO/UMC and regulators. There was a call for a serious look at how the knowledge that has been accumulated by UMC can be used in training young doctors. Members described UMC as a rich resource for reviewing signals.

It was agreed that the next meeting of ACSOAMP should include a discussion on operational aspects related to signals. A future discussion was also requested on crisis prevention and management.

## Smart Safety Surveillance

The WHO pilot project on Smart Safety Surveillance, funded by the Bill & Melinda Gates Foundation (BMGF), will end in 2019. It was noted that the principles of Smart Safety Surveillance are aligned with the principles of 'Smart' regulation of medicinal products; getting 'Pharmacovigilance-ready' for new products ahead of their launch, sharing resources through collaboration, reliance, and recognition of mutual expertise between countries would be the hallmark of this 'Smart' approach. While six countries are being supported through the BMGF grants, funds and resources from other partners (UNITAID, UMC in particular) have been used to integrate the 3S principles in a second set of countries. Members agreed that the principles of 3S should continue to inform the work of the SAV programme. An additional set of countries will be supported in 3S-principles with Global Fund grants in the next phase.

## Country support

SAV Medicines Group has also stepped-up its collaboration with the WHO RSS team in its **Global Benchmarking** activities, to assess the PV systems and functions of the National Regulatory Agency in different Member States. The Institutional Development Plans (IDP) resulting from these assessments will inform the SAV efforts and strategic activities, to allow a systematic, needs-driven technical assistance and support to countries.

Between 2017 and 2018, WHO SAV supported the launch of smart-phone based adverse drug reaction (ADR) reporting tools in Burkina Faso and in Zambia. The objective is to support countries with a smart, integrated application that would not only help ADR reporting, but would also be an effective interface for health-care professionals to access key information on the medicinal products of their interest. In the scale-up phase, WHO is introducing the tool to an additional 8 countries, from different geographic regions. Both MHRA and the UMC are assisting WHO with the relevant technical support.

A number of workshops in **pharmacovigilance inspections** have already been conducted and a practical manual is being developed to support further trainings in this area. The ACSOAMP members advised that the EMA has pharmacovigilance training material and there could be discussions with WHO on how the EMA's resources could be shared with a global audience.

## Prequalification of medicines

Prequalification (PQ) of medicines began in 2001, and PQ of active pharmaceutical ingredients (API) started in 2010. The scope of PQ is now limited to nine therapeutic areas. Since 2018 WHO is piloting biotherapeutic products in its prequalification service.

Two pathways are used in the assessment of products submitted for prequalification: a full assessment pathway or an abridged pathway. In the full assessment pathway, WHO's PQ team fully reviews the quality, safety and efficacy data submitted in the application, inspects finished pharmaceutical products (FPP) and API manufacturing sites to verify compliance with WHO Good Manufacturing Practices, and inspects clinical testing

sites in relation to the product in order to verify compliance with WHO Good Clinical Practices and WHO Good Laboratory Practices.

An abridged assessment pathway is used when WHO recognizes the evaluation of products by Regulatory Agencies that apply standards equivalent to those recommended by WHO. Additional information is required for biopharmaceutical products and for biosimilar products. A WHO-prequalified product will be due for requalification at least every 5 years and will need to meet the corresponding requalification requirements to continue to be prequalified.

The SAV Medicines Group is currently collaborating with the PQ team on a proposed structure for the WHO PQ-specific addendum to the Risk Management Plans for Similar Biopharmaceutical products (SBPs)/biosimilars.

The PQ process is responsible for undertaking a scientific assessment, but does not put the product on the market, nor does it issue a marketing authorization. Some of the procurement agencies supply markets that have no pharmacovigilance facilities. ACSoMP members noted that pharmacovigilance responsibilities would need to be clearly discussed and agreed with sponsors and should be part of the PQ arrangement.

In some countries the manufacturer has no legal obligation to conduct post marketing surveillance.

ACSoMP recommended that it would be useful to learn what the standards/requirements are and who is responsible for surveillance of a particular product in a specific country; WHO should map the requirements and responsibilities for post-marketing surveillance in countries.

### WHO benchmarking and health systems strengthening

Universal healthcare cannot be achieved fully unless people have access to quality-assured health products that are affordable, effective and safe. Universal access therefore depends on effective and efficient regulatory systems. The work that WHO carries out to support Member States in effective and efficient regulation includes the use of the Global Benchmarking Tool (GBT), to identify strengths and gaps, and develop an Institutional Development Plan (IDP) to address the gaps.

WHO uses a five-step capacity-building model, to help National Regulatory Agencies (NRAs) reach a minimum capacity commensurate to a stable, well-functioning and integrated regulatory system.

The GBT has four maturity levels based on ISO 9004. Only 50 countries currently operate at maturity levels 3 ('Stable, well-functioning and integrated regulatory system') and 4 ('Regulatory system operating at advanced level of performance and continuous improvement'). More than half (100) of WHO Member States are still at maturity level 1 ('Some elements of a regulatory system exist'), while 44 countries are at Maturity level 2 ('Evolving national regulatory system that partially performs essential regulatory functions'). Training and support are provided to regulatory experts from low- and middle-income countries, based on needs identified through the IDPs.

SAV has stepped-up its collaboration with the WHO RSS team in its benchmarking activities, to assess the PV systems and functions of the National Regulatory Agency in different Member States. Future benchmarking activities will also include UMC staff on the roster of assessors for PV; the IDPs resulting from these assessments will inform both SAV and UMC efforts in countries.

Members were assured that although the term "benchmarking" implies assessment, the main objective is the IDP where the findings from the assessment are used to move countries forward. In this regard, it would be useful to have alliances or partnerships between mature pharmacovigilance systems and younger ones, once again underscoring the 3S principles, of sharing resources, for cost-effective pharmacovigilance.

The **Coalition of Interested Parties (CIP)** has been established by WHO to coordinate support from development agencies and their funders in its *Regulatory system strengthening* (RSS) work. CIP is a WHO-led partnership in which participation is voluntary and is open to both state and non-state actors. The aim is to bring together all partners that are supporting regulatory systems, to avoid overlap. At the same time, WHO is working with mature NRAs to host placements and hands-on training of regulatory experts from NRAs in low- and middle-income countries (LMICs). The CIP is not a regulatory network but takes account of, and can lend support to, networks of regulatory authorities.

### A global competency and curriculum framework for regulators

WHO and partners have developed a comprehensive global competency framework and curriculum covering key regulatory functions, including pharmacovigilance. Such a framework would benefit NRAs, for example, when recruiting new staff, provide on-the job training and evaluate performance more effectively, and it would benefit individuals who would be able to see a clear skills-development and professional growth in their regulatory work.

The draft global competency framework is aligned with the global benchmarking tool (GBT), and is flexible to allow NRAs at different maturity levels to adapt the framework to fit their context and needs. The framework includes mandatory competencies that form the foundation for success in the world of work, core competencies that are cross-cutting for NRAs corresponding to the regulatory system activities as defined by the GBT, and lastly, role/occupation specific competencies, including vigilance. Further, each competency is classified at three levels according to progression in skill acquisition from (1) advanced beginner, (2) skilled / competent and (3) proficient/expert level.

The draft global competency framework is currently being piloted, with a few NRAs and training providers. The framework will be published for comments before it is finalized.

ACSoMP encouraged further study of the use of the competency model, together with a certification of training.

### Product specific issues

#### Artesunate-pyronaridine (Pyramax)

This is the first artemisinin-based combination therapy (ACT), to be specifically indicated for the blood-stage treatment of malaria due to *P. falciparum* and *P. vivax*. It was granted a positive scientific opinion under the European Medicines Agency (EMA)'s Article 58 procedure in 2012, but to be used only "in the treatment of acute, uncomplicated malaria infection caused by *P. falciparum* or by *P. vivax* in adults and children weighing 20 kg or more, in areas of low transmission with evidence of artemisinin resistance, to be used only as a single treatment course in any given patient". The labelling required systematic liver-enzyme testing before and after treatment because of concerns over hepatotoxicity of the pyronaridine component, and the lack of real-life data on safety following repeat dosing.

In 2015, an EMA Scientific Advisory Group concluded that cumulative safety data on hepatic events yielded sufficient evidence to use artesunate-pyronaridine (Pyramax) for treatment and retreatment of uncomplicated malaria in patients without signs of hepatic injury (including children from 5 kg). This conclusion led EMA to remove all restrictions from the product's label on repeat dosing, on use only in areas of high resistance and low transmission, and on requirements for liver function monitoring. In addition, a positive scientific opinion was granted for artesunate-pyronaridine (Pyramax) granules for the treatment of children of 5-20 kg body weight.

The WHO malaria treatment guidelines (2015) still reflect the previous EMA position. According to the WHO guidelines (2015), in areas with multiple drug resistance where there are few alternatives, the use of artesunate-pyronaridine may be considered. However, it is not recommended for general use; additional data are required on efficacy in children <5 years and safety, especially with repeated dosing.

In the period between May and December 2018, a sub-committee of ACSoMP, together with two expert hepatologists, reviewed all available data on artesunate-pyronaridine (Pyramax), including accumulating data from an ongoing study by the Central Africa Network on Tuberculosis, HIV/AIDS and Malaria (CANTAM) and concluded as follows:

- The role of ACSoMP is not to advise the development of WHO treatment guidelines. Separate WHO procedures and expert committees exist for this purpose. However, the ACSoMP would make recommendations based on safety review of specific products for the consideration of WHO disease programmes and through them, to the relevant guideline development committees.
- Taking into account all the available and accumulating evidence, ACSoMP recommends that the current safety restrictions in the WHO malaria treatment guidelines (2015), on the use of artesunate-pyronaridine (Pyramax) in the treatment of uncomplicated malaria, are no longer justified.
- In view of the limited clinical use of the product, the lack of safety data from clinical use is notable, particularly in vulnerable patients with comorbidities.
- The absence of evidence in subgroups strongly supports the need for active, robust surveillance of the product once used in a wider setting. This could be through enhanced spontaneous reporting or observational cohort studies. Specific advice on the design of such surveillance could be sought from the ACSoMP.
- The benefit-risk balance of a medicinal product depends very much on the clinical context of its use, and the ability of the environment in which it is being used to recognize risks and manage them effectively. This requires a stable and well-performing safety surveillance system embedded in a regulatory infrastructure that allows prompt, risk-minimizing actions when needed. These aspects need to be taken into consideration in the roll out of artesunate-pyronaridine (Pyramax).

- In general, WHO should ensure that medicinal products that it endorses for use are actively monitored. This would likely involve WHO collaboration with other organizations and could ensure that relevant information about the benefits and risks of the product is collated and assessed, to advise WHO policy.

### **Bedaquiline**

Active TB drug-safety monitoring and management (abbreviated as aDSM) describes a WHO TB programme component to provide for the active and systematic clinical and laboratory assessment of patients on treatment for XDR-TB, or with new TB drugs or novel MDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.

The aDSM 'database' aims to

- (1) facilitate the collection, harmonization and pooling of data from different sources for the surveillance of TB drug safety,
- (2) enable early detection of potential safety signals, and
- (3) use the information, in addition to information collected in the WHO Global ICSR database, Vigibase and/or collected through other channels, to inform treatment guidelines for specific populations.

The contributing country is the owner of the data in aDSM database; WHO collects the data for analysis but does not give data-access to third parties; standard channels of communication need to be maintained between national pharmacovigilance programmes and the national aDSM database. The objective of the WHO analysis of the data is to generate evidence to support TB patient treatment guidelines.

Sixteen countries have so far reported data, from 889 patients, to the aDSM database, with 891 adverse events reported from 14 countries. A 2018 analysis of 418 SAEs, that reviewed a treatment regimen (containing BDQ or not) and different associations, did not identify any safety concerns /signals.

ACSoMP commended the WHO Global TB programme, GTB, for developing structured pharmacovigilance around a very important product used to treat a serious disease. The Committee advised integrating the aDSM data in Vigibase, to allow broader analysis, and recommended a more rigorous evaluation of the data in the aDSM database by a group of pharmacovigilance experts.

### **Dolutegravir**

In April 2018, an update on WHO ARV toxicity monitoring work was presented at the 15th meeting of ACSoMP where it was highlighted that with dolutegravir (DTG), there were remaining gaps in safety data in pregnancy and breastfeeding. In May 2018 new data were published from a large observational study of birth outcomes since 2014 in Botswana (the Tsepamo study), showing a potential association between DTG use at the time of conception and an increased risk in neural tube defect (NTD) in infants born of women who were taking DTG at the time of conception. In August 2018, a subcommittee of ACSoMP was set up, to review all available data on DTG, to refute or confirm the safety signal.

The DTG subcommittee's latest meeting had been on 6 May 2019 just prior to the 16th meeting of ACSoMP. The report and recommendations of the DTG sub-committee were presented by the chair to ACSoMP members.

The prevalence of NTD with periconception DTG in the Tsepamo surveillance study has significantly declined from 0.94% (95% CI 0.38, 2.4%) in May 2018 to 0.30% (95% CI 0.13, 0.69%) in March 2019. However, the NTD prevalence difference between periconception DTG and each of the other exposure groups, including non-DTG ART or EFV ART from conception (0.10% and 0.03%, respectively), or DTG or non-DTG started in pregnancy (0.03% and 0.05%, respectively), and HIV-uninfected women (0.08%) (all of which have remained stable over time), remains statistically significantly elevated.

From an extensive review of the literature, only one other NTD has been reported with periconception DTG in 247 prospective exposures (0.35%) from the U.S. However, outside of the Tsepamo study, the majority of data come from countries with food folate fortification, and hence, a lower background NTD prevalence and higher numbers of exposures are required to refute an association.

The sub-committee noted that, in the Tsepamo study the adverse pregnancy outcomes (miscarriage, stillbirth, preterm birth, low birth weight, small for gestational age, neonatal mortality) other than neural tube defects do not appear to be increased with periconception DTG use compared to periconception non-DTG ART or ART started during pregnancy.

Continued surveillance is needed to more definitively confirm or refute the NTD signal, and a number of studies are ongoing to address this. If the NTD signal currently observed in Tsepamo is confirmed, although it

is three-times higher than other populations, the absolute risk is very low, 0.30% - a risk difference of 2 excess NTD per 1000 periconception exposures.

While there are some suggestive findings, there is no definitive pathogenic mechanism for NTD with periconception DTG exposure. Evaluation of the available basic science studies by experts in the field would be very useful.

The ACSoMP subcommittee strongly supports continuation of the Tsepamo birth surveillance study, not only to provide a definitive answer to the question of a NTD signal, but also as a general model for studying the safety of drugs in pregnancy. The collaborative effort of the subcommittee members from a range of institutions was considered an excellent model of bringing a relevant and up-to-date critical appraisal of drug safety from ACSoMP to the WHO's Guideline Development Group.

### **Fexinidazole**

ACSoMP received a proposal for a post-authorization safety study of fexinidazole for human African trypanosomiasis (HAT) based on the secondary use of data prospectively collected by WHO in selected sub-Saharan African countries. The EMA gave a positive opinion for fexinidazole (Winthrop) on 15 November 2018 in accordance with its Article 58, which does not authorize the product for use in the EU but provides a scientific expert opinion on the safety and efficacy of the product for use.

An alternative name for HAT is sleeping sickness which, if untreated, is almost always lethal over time. WHO began to target the disease for elimination in 2012. Five medicines can be used, are effective but are logistically difficult to administer, especially in second stage HAT with a regime of intravenous administration twice a day for 7 days combined with an oral drug. Fexinidazole is taken in a 10-day oral course which has advantages over injectable administration but also leads to potential problems of compliance. Additionally, there are some new disadvantages in that fexinidazole must be taken with food (solid not liquid) in the stomach, otherwise the absorption is 3-fold lower. There are also problems of vomiting (42%, and up to 69% in children), nausea (35%) and psychiatric events such as insomnia, psychotic symptoms, depression and anxiety (32%), which may further affect compliance.

EMA has asked Sanofi, the manufacturer, to conduct a phase 3 post-authorization safety study of fexinidazole. Additionally, WHO wishes to monitor real-life effectiveness. Training of staff is mandatory for administering fexinidazole, and pharmacovigilance can be included in the same training. A protocol for the 16-country study has been drafted by Sanofi, to study safety in real-life conditions plus effectiveness at 12 and 24 months of follow-up.

It was agreed to set up a small group of experts from ACSoMP, together with an independent disease specialist, to review and provide input to the study protocol.

The protocol would be reviewed by PRAC and the study will begin in the third quarter of 2019. Fexinidazole has also been submitted for inclusion in WHO's Essential Medicines List.

### **Tafenoquine**

More than one-third of the world's population is at risk of *Plasmodium vivax* (*P. vivax*) malaria, the second most common species of malaria. For the treatment of *P. vivax* malaria, WHO recommends standard antimalarial medicines followed by a 14-day regimen of primaquine to prevent relapses of the disease. Though primaquine is highly effective, patients are required to take daily doses of the medicine for a full 2-week period. As such, treatment compliance is a challenge.

A new medicine, tafenoquine, offers fresh hope in global efforts to combat *P. vivax* malaria. Due to its long half-life, tafenoquine has the distinct advantage of being a single-dose treatment, thereby increasing the likelihood of treatment compliance. It was recently approved by 2 regulatory agencies, the US FDA and the Australian Therapeutic Goods Administration (TGA), for adults 16 years of age and older.

There is, however, a key safety challenge associated with both tafenoquine and primaquine. Among patients who have a deficiency of the enzyme G6PD (glucose-6 phosphate dehydrogenase) – a genetic condition with a prevalence of up to 35% in some countries affected by *P. vivax* malaria – the drugs can trigger a severe blood disorder known as acute haemolytic anaemia. Primaquine, which is eliminated in a matter of hours, can be stopped if symptoms and signs of haemolysis occur. But tafenoquine remains in the blood for several days, and haemolysis could continue for days in patients with G6PD deficiency if given tafenoquine. A precise measurement of G6PD status (quantitative) is required before initiating treatment with tafenoquine. At present, quantitative G6PD tests are only accessible in well-resourced laboratory settings; such tests are not readily available in resource limited countries affected by *P. vivax* malaria. In these settings the introduction of tafenoquine should be accompanied by a WHO prequalified point-of-care quantitative G6PD test.

Several point-of-care quantitative G6PD tests are either under development or have recently entered the market; some are expected to be submitted by manufacturers for review by WHO's prequalification team in late 2019. WHO guidance around the use of tafenoquine for the treatment of *P. vivax* malaria will be developed in parallel, with a review of G6PD point-of-care quantitative tests. The guidance will be developed in an independent, comprehensive and efficient manner through a collaborative process that involves the three levels of the Organization and multiple departments.

The Advisory Committee was briefed on the above developments. Members noted that the complexities of this process made for an extremely challenging situation.