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Organization

# WHO Pharmaceuticals **NEWSLETTER**

2023

No. **2**

**WHO Vision for Safety of  
Medicinal Products  
No country left behind:  
worldwide pharmacovigilance  
for safer medicinal products,  
safer patients**

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

**Pharmacovigilance,  
MHP/RPQ,  
World Health Organization,  
1211 Geneva 27, Switzerland,  
E-mail address:  
pvsupport@who.int**

*This Newsletter is also available at:  
<https://www.who.int/teams/regulation-prequalification>*

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicinal products and regulatory actions taken by authorities around the world.

In addition, this edition includes summary and recommendations from the second joint meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP), held from 14–16 December 2022.

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## Acetaminophen

### Risk of drug-induced hypersensitivity syndrome

**Japan.** The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for acetaminophen should be revised to include the risk of drug-induced hypersensitivity syndrome.

Acetaminophen products are in the form of oral dosage forms, suppositories or injections. They contain acetaminophen only or combination with other antipyretics, and sold as prescription or over-the-counter medicines.

The MHLW and PMDA assessed 48 cases of domestic adverse event reports involving acetaminophen and drug-induced hypersensitivity syndrome, and in six cases a causal relationship between the drug and event was reasonably possible. The MHLW and PMDA concluded that drug-induced hypersensitivity syndrome should be added as a clinically significant adverse reaction.

Health-care professionals are advised that symptoms of drug-induced hypersensitivity syndrome initially manifest as rash and pyrexia, followed by serious delayed symptoms of hypersensitivity accompanied by hepatic impairment, swollen lymph nodes, increased eosinophil counts and appearance of atypical lymphocytes. Symptoms are often accompanied by virus reactivation, such as human herpes virus type 6 (HHV-6). Recipients should be alerted for recurrence or prolongation of

rash, pyrexia, and hepatic impairment, etc. that may occur even after discontinuation of administration.

#### Reference:

Revision of Precautions, MHLW/PMDA, 17 January 2023 ([link1](#) and [link2](#) to the source within [www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Cephalosporins

### Risk of seizures

**Canada.** Health Canada has announced that the product safety information for cephalosporins will be updated to include the risk of seizures in all the cephalosporins. As the risk of seizures has been already included for some cephalosporins, this update applies to cephalosporins that do not currently include this risk.

Cephalosporins are a group of prescription antibiotic medicines (cephalexin, cefazolin, cefadroxil, cefoxitin, cefuroxime, cefprozil, cefotaxime, ceftazidime, ceftriaxone, cefixime, cefepime, ceftobiprole and ceftolozane-tazobactam) and are indicated for the treatment of a wide range of bacterial infections.

Triggered by a US Food and Drug Administration update to the product safety information for cefazolin to include the risk of seizures, Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, as well as medical and scientific literature. Health Canada reviewed 84 cases (7 domestic and 77 international) of seizures in patients taking cephalosporins. Of the 84

cases, 13 cases (all international) were found to be probably linked to the use of cephalosporins, and 62 cases (4 domestic and 58 international) were found to be possibly linked. Three cases (all international) were unlikely to be linked to the use of cephalosporins. Six cases (3 domestic and 3 international) could not be assessed. The review concluded that there may be a link between the use of cephalosporins and the risk of seizures.

#### Reference:

Summary Safety Review, Health Canada, 23 January 2023 ([link](#) to the source within [www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

## Colistimethate injection

### Risk of pseudo-Bartter syndrome (PBS)

**Europe.** The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended a change to the product information for colistimethate injection to include risk of pseudo-Bartter syndrome (PBS). PBS is defined as hypokalaemic hypochloraemic metabolic alkalosis in the absence of renal tubular pathology.

Colistimethate injection is an antibiotic belonging to a group of polymyxins, indicated for the treatment of certain bacterial infections.

The PRAC reviewed few case reports of PBS reported in children and adults with the intravenous use of colistimethate in the literature and recommended the

amendment of the product information to include this risk.

Health-care professionals are advised that serum electrolytes should be monitored in suspected cases and appropriate clinical case management should be initiated. However, normalization of electrolyte imbalance might not be achieved without discontinuation of colistimethate. If patients experience muscle spasm, fatigue or increased urine output at any time, they should inform their doctor immediately as these events may be related to PBS.

#### Reference:

PRAC recommendations on signals, EMA, 6 March 2023 ([link to the source within www.ema.europa.eu](https://www.ema.europa.eu))

## Finasteride

### Risk of suicidal ideation and self-injury

**Canada.** Health Canada has announced that the product safety information for finasteride will be updated to strengthen warnings on the risks of suicidal ideation and self-injury.

Finasteride is indicated for the treatment and control of prostate enlargement and for the treatment of male pattern hair loss (androgenetic alopecia).

Triggered by the publication of a media article that discussed the potential risk of suicide in patients using finasteride for male pattern hair loss, Health Canada reviewed the available information.

- Data from the Canada Vigilance database indicated

401 cases (29 domestic and 372 international) of suicide, suicidal ideation and/or self-injury in patients using finasteride were found. Of the 401 cases, 25 cases (10 domestic) met the criteria for further assessment, and 23 cases (9 domestic) were found to be possibly linked to the use of finasteride.

- In the scientific literature, there was a growing body of scientific evidence showing the association between the use of finasteride and the risks of suicide, suicidal ideation and self-injury.

The review found a possible link between the use of finasteride and the risks of suicidal ideation and self-injury. Currently, there is not enough information to establish a link between the use of finasteride and the risk of suicide.

Health-care professionals are advised to screen patients for psychiatric risk factors prior to starting treatment, as well as continuous patient monitoring during and after stopping treatment.

#### Reference:

Summary Safety Review, Health Canada, 19 January 2023 ([link to the source within www.hc-sc.gc.ca](https://www.hc-sc.gc.ca))

(See also WHO Pharmaceuticals Newsletter No.4 2022: *Finasteride and Potential risk of suicidal ideation in Singapore*, No.2, 2019: *the same title in Canada*)

## Gemifloxacin

### Cancellation of registration

**Egypt.** The Egyptian Pharmacovigilance Center (EPVC), Egyptian Drug Authority (EDA) has announced that the registration of products containing

gemifloxacin is cancelled.

Gemifloxacin is a quinolone antibiotic and is indicated for the treatment of bronchitis and pneumonia caused by bacterial infections.

The technical committee of the EDA found the risk-benefit balance of gemifloxacin no more favorable due to the potential genotoxicity of gemifloxacin and the availability of safer quinolone products in the Egyptian market. The committee decided to cease the marketing of products.

#### Reference:

Newsletter, EDA, January 2023 ([link to the source within www.edaegypt.gov.eg](https://www.edaegypt.gov.eg)) (See also WHO Drug Information No.3 2009: *Gemifloxacin: withdrawal of marketing authorization application in Europe*)

## Glucagon-like peptide-1 (GLP-1) receptor agonists

### Risk of cholecystitis, cholangitis and cholestatic jaundice

**Japan.** The MHLW and PMDA have announced that the product information for Glucagon-like peptide-1 (GLP-1) receptor agonists should be revised to add the risk of cholecystitis, cholangitis and cholestatic jaundice (acute gallbladder diseases).

GLP-1 receptor agonists include the following medicines: exenatide (Byetta®, Bydureon®), semaglutide (Ozempic®, Rybelsus®), dulaglutide (Trulicity®), lixisenatide (Lyxumia®), insulin glargine/lixisenatide (Soliqua®), liraglutide

(Victoza®), insulin degludec/liraglutide (Xultophy®) and tirzepatide (Mounjaro®), all in the form of subcutaneous injection except semaglutide (Rybelsus®) as tablet. Cholelithiasis is a known adverse reaction to these medicines that are indicated for the treatment of type 2 diabetes mellitus. .

The MHLW and PMDA assessed 48 domestic cases of adverse event reports involving GLP-1 receptor agonists and the events. In 17 cases, a causal relationship between the medicine and event was reasonably possible. Although the event reporting and causal possibility were not made for all GLP-1 receptor agonists, the pharmacological mechanism, such as inhibition of gallbladder contraction, was considered to promote gallstone formation and cause acute gallbladder disease as a class-effect. The MHLW and PMDA concluded that cholecystitis, cholangitis and cholestatic jaundice should be added as clinically significant adverse reactions, in addition to cholelithiasis.

Health-care professionals should consider close investigation of the cause, including imaging tests, if abdominal symptoms such as abdominal pain are observed in patients.

#### Reference:

Revision of Precautions, MHLW/PMDA, 14 February 2023 ([link1](#), [link2](#) and [link3](#) to the source within [www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Hydroxychloroquine

### Risk of acute febrile neutrophilic dermatosis

#### (Sweet's syndrome)

**Japan.** The MHLW and PMDA have announced that the product information for hydroxychloroquine (Plaquenil®) should be revised to add the risk of acute febrile neutrophilic dermatosis (Sweet's syndrome).

Hydroxychloroquine is indicated for the treatment of cutaneous lupus erythematosus and systemic lupus erythematosus.

The MHLW and PMDA assessed six cases of adverse event reports (one domestic and five international) involving hydroxychloroquine and the event, and in four international cases a causal relationship between the medicine and event was reasonably possible. The MHLW and PMDA concluded that acute febrile neutrophilic dermatosis (Sweet's syndrome) should be added as a clinically significant adverse reaction.

#### Reference:

Revision of Precautions, MHLW/PMDA, 17 January 2023 ([link to the source within www.pmda.go.jp/english/](#))

## Hydroxyethylated starch

### Contraindication in patients with severe sepsis and other conditions

**1. Japan.** The MHLW and PMDA have announced that the product information for hydroxyethylated starch (HES) should be revised to indicate its contraindication in patients with severe sepsis.

HES are infused as blood substitutes that increase the

plasma volume based on colloid osmotic effects and used for maintenance of circulating blood volume.

The suspension of marketing authorizations of HES in the EU in May 2022 due to its continued use outside the recommendations in the product information triggered the review by MHLW and PMDA. The MHLW and PMDA reviewed the available information including the results of clinical trials, drug utilization studies, adverse events reporting in Japan and views from the relevant physicians associations. In contrast to EU, the off-label use of HES outside the recommendation and subsequent adverse events were rarely observed in Japan. The review concluded that the marketing of HES can be continued. However, further warnings are necessary for use in patients with sepsis where an increased risk was confirmed from the literature.

In the revised product information, use in patients with severe sepsis is contraindicated, and use in non-severe sepsis patients requires careful administration. Severe sepsis is defined as having an infection meeting the systemic inflammatory response syndrome (SIRS) criteria and having at least one organ dysfunction (= sequential organ failure assessment (SOFA) score of 3 or more).

#### Reference:

Revision of Precautions, MHLW/PMDA, 12 January 2023 ([link1](#), [2](#), and [3](#) to the source within [www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

**2. Egypt.** The EPVC, EDA has issued Direct Healthcare Professional Communication (DHPC) to remind health-care professionals of safety measures to minimize the risk of kidney injury and death from HES.

In 2013 the use of HES was restricted because of an increased risk of kidney injury and mortality in certain patient populations. Despite extensive measures in place to protect vulnerable patient populations, final results of a drug utilization study have shown continued high non-adherence to the product information including non-adherence to contraindications. According to the EDA technical committee decision, HES must not be used in patients with sepsis, kidney impairment, burns or critically ill patients.

Health-care professionals should ensure proper and safe use of HES according to their approved product information (the treatment of hypovolaemia in adults and children only if crystalloids are not sufficient to stabilize the patient, and if the anticipated benefit justifies the risk).

**Reference:**

Newsletter, EDA, February 2023 ([link to the source within www.edaegypt.gov.eg](http://www.edaegypt.gov.eg))

(See also WHO Pharmaceuticals Newsletter [No.2 2022](#): Hydroxyethyl-starch solutions for infusion and Risk of kidney injury and death in Europe)

## Oral live attenuated human rotavirus vaccine

### Risk of anaphylaxis

**Japan.** The MHLW and PMDA

have announced that the product information for oral live attenuated human rotavirus vaccine (Rotarix®) should be revised to add the risk of anaphylaxis.

Oral live attenuated human rotavirus vaccine is indicated for the prevention of gastroenteritis caused by rotavirus.

The MHLW and PMDA assessed 28 cases of domestic adverse event reports involving the vaccine and anaphylaxis, and in two cases a causal relationship between the vaccine and event was reasonably possible. The MHLW and PMDA concluded that anaphylaxis should be added as a clinically significant adverse reaction.

**Reference:**

Revision of Precautions, MHLW/PMDA, 17 January 2023 ([link to the source within www.pmda.go.jp/english/](http://www.pmda.go.jp/english/))

## Pholcodine

### Prior use of pholcodine-containing cough and cold remedies and risk of perioperative anaphylactic reactions to neuromuscular blocking agents (NMBAs)

**WHO.** WHO is alerting health-care professionals and regulatory authorities of the risk of anaphylactic reactions in people who have taken pholcodine-containing products at least 12 months prior to surgical procedures involving the administration of general anaesthesia with neuromuscular blocking agents (NMBAs). Some regulatory authorities have taken decisions to withdraw pholcodine-containing products

from their markets to address this risk.

Pholcodine is an opioid medicine and is used in adults and children to treat non-productive (dry) coughs. Several preparations are readily available and commonly used as over-the-counter tablets and syrups globally.

The European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee reviewed all available evidence including post-marketing safety data, information from third parties such as health-care professionals, and final results of a French multicentre case-control study comparing pholcodine exposure within a year before anaesthesia between patients with NMBA-related perioperative anaphylactic reactions.<sup>1</sup> The available data showed that the use of pholcodine in the 12 months before general anaesthesia with NMBAs is a risk factor for developing an anaphylactic reaction (a sudden, severe and life-threatening allergic reaction) to NMBAs.

Based on the lack of effective measures to minimize the risk, the lack of an identified patient population for whom the benefits of pholcodine outweigh its risks, and the seriousness of the safety risk, the European Commission issued a legally binding decision applicable in all EU Member States to withdraw pholcodine containing products.<sup>2</sup>

As of 29 March 2023, at least three other regulatory authorities had withdrawn prescription and over-the-counter preparations

containing pholcodine from their markets: the Therapeutic Goods Administration (TGA), Australia, the Medicines and Healthcare products Regulatory Agency (MHRA), the United Kingdom, and the National Pharmaceutical Regulatory Agency (NPRA), Malaysia.<sup>3 4 5</sup>

Advice to health-care professionals and consumers is provided by the TGA and other authorities as follows:

For health-care professionals:

- Advise patients to stop taking pholcodine-containing medicines and consider appropriate alternatives to treat their symptoms.
- Check whether patients scheduled to undergo general anaesthesia with NMBA have used pholcodine in the previous 12 months and remain aware of the risk of anaphylactic reactions in these patients.

For consumers:

- Check if any of your over-the-counter cold and flu medicines contain pholcodine. Pholcodine is particularly used in cough lozenge (tablet) or syrup products but can be found in other medicines. If they do, ask your doctor or pharmacist to suggest an alternative treatment.
- If you need general anaesthesia and have taken pholcodine in the past 12 months, tell your health professional prior to the procedure. It may help to show this safety alert to your doctor.

WHO is issuing this safety alert in view of the wide use of

pholcodine-containing products globally and the seriousness of potential anaphylactic reactions. The information was also previously covered by WHO in its Pharmaceuticals Newsletter. Additionally, the WHO has received individual case safety reports (ICSRs) of anaphylactic reactions in VigiBase (the WHO global database of ICSR) from different countries following the administration of pholcodine and NMBA.

**Reference:** Safety alert, WHO, 31 March 2023 ([link to the source within \*www.who.int\*](#))

(See also WHO Pharmaceuticals Newsletter [No.1 2023](#): Withdrawal of pholcodine medicines from EU market in Europe, [No.4, 2022](#): Pholcodine and Potential risk of developing anaphylactic reactions to NMBA in Europe)

## Rocuronium

### Risk of mydriasis

**Canada.** Health Canada has announced that the product safety information for rocuronium will be updated to include the risk of mydriasis.

Rocuronium is used to relax muscles during surgery as part of the general anaesthesia and to facilitate assisted breathing (mechanical ventilation) in patients requiring intensive care. Rocuronium is available as a solution for injection, is administered by a healthcare professional and is usually used in a hospital setting.

Triggered by international case reports published in the literature concerning this risk, Health Canada reviewed information provided by manufacturers, foreign regulatory agencies and from searches of the Canada

Vigilance database and published literature.

- Health Canada reviewed nine international cases of mydriasis in patients administered rocuronium. Of the nine cases assessed, three cases were found to be probably linked to the use of rocuronium, and two cases were found to be possibly linked.
- In the published literature, there were articles explaining how rocuronium may lead to mydriasis.

The review found a link between the use of rocuronium and the risk of mydriasis in mechanically ventilated adult patients with systemic infection and in newborn infants undergoing surgery. Mydriasis usually reverses when rocuronium is discontinued.

### Reference:

Summary Safety Review, Health Canada, 9 February 2023 ([link to the source within \*www.hc-sc.gc.ca\*](#))

## Statins

### Potential risks of myasthenia gravis and ocular myasthenia

**Europe.** The PRAC has recommended a change to the product information for statins to include potential risks of myasthenia gravis and ocular myasthenia.

Statins are HMG-CoA reductase inhibitors and include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular

myasthenia. Treatment with statins should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

#### Reference:

PRAC recommendations on signals, EMA, 6 February 2023 ([link to the source within www.ema.europa.eu](#))

## Tazobactam and piperacillin

### Risk of haemophagocytic lymphohistiocytosis

**Japan.** The MHLW and PMDA have announced that the product information for tazobactam and piperacillin (Zosyn® and the others) should be revised to add the risk of haemophagocytic lymphohistiocytosis (haemophagocytic syndrome).

Tazobactam and piperacillin, a combination medicinal product for injection, is indicated for the treatment of infections mainly from gram-positive and gram-negative bacteria.

The MHLW and PMDA assessed 41 cases of adverse event reports (15 domestic and 26 international) involving tazobactam and piperacillin and the event. In five domestic cases and three international cases a causal relationship between the medicine and event was reasonably possible. The MHLW and PMDA concluded that haemophagocytic lymphohistiocytosis should be added as a clinically significant adverse reaction.

Health-care professionals should carefully monitor

patients, and discontinue administration of this medicine and initiate appropriate measures if abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed.

#### Reference:

Revision of Precautions, MHLW/PMDA, 14 February 2023 ([link1](#) and [link2](#) to the source within [www.pmda.go.jp/english/](#))

## Third generation aromatase inhibitors

### Risk of tendon disorders

**Canada.** Health Canada has announced that the product safety information for third generation aromatase inhibitors (anastrozole, exemestane and letrozole) will be updated to include the risk of tendon disorders. Tendon disorders include tendon inflammation (tendonitis), inflammation of the tendon sheath (tenosynovitis) and tendon tears (tendon rupture).

Third generation aromatase inhibitors are indicated for the treatment of breast cancer in women who have attained menopause.

Triggered by an update including the risks of tendonitis and tendon rupture by the EMA to letrozole product safety information, Health Canada reviewed the following information.

- Reports of events of tendonitis and tenosynovitis and its potential relation to tendon rupture in five

randomized controlled trials (RCTs),

- In 25 case reports (2 domestic and 23 international) of tendon rupture (10 cases) and tendonitis (15 cases), a link between the risk of tendon rupture and tendonitis with the use of a third generation aromatase inhibitor could not be ruled out. However, these case reports included other medications and/or conditions that could have contributed to the reported adverse events.

The review concluded that there is likely a link between the use of third generation aromatase inhibitors and the risks of tendonitis and tenosynovitis. Also, a link with tendon rupture could not be ruled out.

#### Reference:

Summary Safety Review, Health Canada, 17 January 2023 ([link to the source within www.hc-sc.gc.ca](#))

## Ceftriaxone and cefotaxime

### Risk of severe hypersensitivity reaction

**Egypt.** The EPVC, EDA has issued DHPC to remind health-care professionals of safety measures to minimize the risk of severe hypersensitivity reaction, anaphylaxis and other life-threatening adverse events.

Ceftriaxone and cefotaxime are antibiotics indicated for the treatment of various infections, and are strictly contraindicated in patients with history of immediate type hypersensitivity to cephalosporins.

The EPVC received reports of hypersensitivity, anaphylaxis and other life-threatening adverse events which could be linked to these medicines administered improperly or without sensitivity testing.

Prior to administration, Health-care professionals should verify if the patient has had previous hypersensitivity reactions to cefotaxime sodium, ceftriaxone, cephalosporins, penicillin, or other medicine. A sensitivity test should be performed before each dose. It is recommended to administer these medicines in hospital settings with preparations for emergency measures.

#### Reference:

Newsletter, EDA, January 2023 ([link to the source within www.edaegypt.gov.eg](#))

## Dabrafenib

### Potential risk of disseminated intravascular

## coagulopathy (DIC)

**Saudi Arabia.** The Saudi Food & Drug Authority (SFDA) has released a safety signal concerning dabrafenib (Tafinlar®) and the potential risk of disseminated intravascular coagulopathy (DIC). DIC is characterized by the widespread activation of coagulation resulting in the intravascular formation of fibrin and ultimately thrombotic occlusion of small and midsize vessels

Dabrafenib is an antineoplastic medicine indicated for the treatment of melanoma and non-small cell lung cancer (NSCLC).

The SFDA reviewed 21 ICSRs involving dabrafenib and DIC that were reported in Vigibase. The WHO-UMC causality assessment criteria were applied on 13 cases (completeness score 0.5 and above), and two cases provided positive association (2 possible cases). Datamining indicated positive association (IC=2.4) in Vigibase. Additionally, evidence from two case-reports published in the literature were supportive for this signal.

The SFDA's review concluded that the current available evidence might support a relationship between dabrafenib and DIC.

This signal needs further investigation to confirm the risk; however, health-care professionals should be aware of this potential adverse reaction.

#### Reference:

Safety Alerts, SFDA, 23 October 2022 ([link to the source within www.sFDA.gov.sa](#))

## Erenumab

### Potential risk of Raynaud's phenomenon

**Saudi Arabia.** The SFDA has released a safety signal concerning erenumab (Aimovig®) and the potential risk of Raynaud's phenomenon.

Raynaud's phenomenon is vasospastic disorder recognized by transitory, episodic, and reversible vasospasm of peripheral blood vessels and characterized by color changes ranging from white caused by constriction of digital arteries (ischemic phase) to bluish-cyanotic (cyanotic phase) and ultimately to red due to vasodilation (hyperemic phase).

Erenumab is IgG2 monoclonal antibody produced and is indicated for migraine prophylaxis.

The SFDA reviewed 58 ICSRs involving erenumab with Raynaud's phenomenon that were reported in Vigibase. The WHO-UMC causality assessment criteria were applied on 13 cases (completeness score 0.6 and above), and eight cases provided positive association (1 probable case and 7 possible cases). Datamining indicated positive association (IC=3.1) in Vigibase. Additionally, evidence from one review article and one case-report in the literature was supportive for this signal.

The SFDA's review concluded that the current available might support a relationship between erenumab and Raynaud's phenomenon.

Health-care professionals should be aware of this

potential risk and are advised to monitor any signs or symptoms in treated patients.

#### Reference:

Safety Alerts, SFDA, 23 October 2022 ([link to the source within www.sfda.gov.sa](#))

## Isotretinoin

### Potential risk of blood growth hormone decreased (BGHD)

**Saudi Arabia.** The SFDA has released a safety signal concerning isotretinoin (oral dosage form, Roaccutane®) and the potential risk of blood growth hormone decreased (BGHD).

Isotretinoin is a retinoid and derivative of vitamin A and its oral dosage form is indicated for the systemic treatment of acne.

The SFDA reviewed five ICSRs involving isotretinoin (oral dosage form) and BGHD that were reported in VigiBase. The WHO-UMC causality assessment criteria were applied, and there was one possible case (the other four cases were not assessable). Datamining indicated positive association (IC= 2.7) in VigiBase. Additionally, evidence from a multi-center study in the literature was supportive for this signal.

The SFDA's review concluded that the current available evidence might support a relationship between isotretinoin and BGHD.

Health-care professionals should be aware of this potential risk and are advised to monitor any signs or symptoms in treated patients.

#### Reference:

Safety Alerts, SFDA, 23 October 2022 ([link to the source within www.sfda.gov.sa](#))

## Miltefosine

### Measures to minimize the risk of ocular adverse events

**WHO.** WHO is alerting health-care professionals and regulatory authorities of the risk of ocular adverse events in people who have taken miltefosine and providing advice of measures to minimize this risk in patients exposed to miltefosine.

Miltefosine is an oral anti-infective and one of the medicines with established efficacy in the treatment of some forms of leishmaniasis, a parasitic infection spread by the bite of infected female phlebotomine sandflies. Leishmaniasis can take different clinical forms, including cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL).

Following reports of ocular disorders following miltefosine use originating mostly from South-Asia, the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) had recommended WHO to further investigate this issue.<sup>1</sup> Based on the available data, the WHO ad-hoc Multidisciplinary Technical Group (MTG) considered that a causal relationship between ocular adverse events and the exposure to miltefosine is at least a reasonable possibility. The risk of ocular adverse events, such as redness of the eye, inflammation of different

eye structures (keratitis, scleritis, uveitis) and visual impairment up to blindness has been observed mostly during the treatment of patients with Post-Kala-Azar Dermal Leishmaniasis (PKDL) in South Asia in both men and women, including in children under 18-year-old, and mostly beyond 28 days of treatment. No further risk factor could be identified. When the information was available, most of the cases resolved after miltefosine was withdrawn, sometimes after a symptomatic treatment was started. However, in some cases, the adverse ocular event led to permanent loss of sight. The frequency of adverse ocular events during treatment with miltefosine could not be estimated based on the available data, and the mechanism of action remains unclear.

Information for health-care professionals includes:

- Before starting the miltefosine treatment the history of eye disorders should be collected and an eye examination should be done as appropriate.
- In case of current or past history of ocular disorder, the benefits and the risks of treating a patient with miltefosine should be carefully considered, and advice from an ophthalmologist should be sought where feasible.
- All patients should be informed before starting the treatment that in case of eye problems during the treatment (e.g., red eyes, increased watering, eye pain, blurred vision) they should discontinue miltefosine and

contact their healthcare professional immediately.

- If ocular complications occur and a connection with miltefosine cannot be excluded, miltefosine should be discontinued immediately and an alternative treatment for leishmaniasis should be initiated if necessary. Since miltefosine has a very long half-life (>6 days), it is possible that ocular changes will not be reversible without treatment even after discontinuation of miltefosine. Therefore, an eye specialist should be consulted in such cases to avoid the possibility of permanent damage.

Full information including the Guiding principles for prevention, early detection and management of eye complications in patients treated with miltefosine is provided in the link below.

**Reference:** Safety alert, WHO, 12 April 2023 ([link to the source within \*www.who.int\*](#))

(See also ACSoMP recommendation on miltefosine in Features of this edition (page 15).)

## Mycophenolic acid

### Potential risk of posterior reversible encephalopathy syndrome (PRES)

**Saudi Arabia.** The SFDA has released a safety signal concerning mycophenolic acid and the potential risk of posterior reversible encephalopathy syndrome (PRES).

PRES presents with rapid onset of symptoms including headache, seizures, altered consciousness, and visual disturbance and may accompany acute hypertension.

Mycophenolic acid is an immunosuppressant to prevent organ rejection after hepatic, renal, or cardiac transplants used in combination with cyclosporine and corticosteroids.

The SFDA reviewed 198 ICSRs involving mycophenolic acid and PRES that were reported in Vigibase. The WHO causality assessment criteria were applied on 18 cases (completeness score 0.7 and above), and five cases provided positive association (possible cases). Datamining indicated positive association (IC=4.5) in Vigibase. Additionally, evidence from two case-reports in the literature was supportive for this signal.

The SFDA's review concluded that the current available evidence might support a relationship between mycophenolic acid and PRES.

Health-care professionals should be aware of this potential risk and are advised to monitor any signs or symptoms in treated patients.

#### Reference:

Safety Alerts, SFDA, 23 October 2022 ([link to the source within \*www.sfd.gov.sa\*](#))

## Onasemnogene abeparvovec

### Risk of acute liver failure

**Europe.** The EMA has published a direct health-care professional communication (DHPC) on onasemnogene abeparvovec (Zolgensma®) about recent reports of fatal cases of acute liver failure in patients treated with this medicine. EMA also updated

recommendations for monitoring liver function, assessing suspected liver injury after infusion and advice regarding tapering the corticosteroid treatment.

Onasemnogene abeparvovec is a gene therapy medicine and is indicated for the treatment of spinal muscular atrophy (SMA).

Patients with worsening liver function tests and/or signs or symptoms of acute liver illness should be promptly assessed and treated with corticosteroids. If they don't respond, the treating physician should consult a paediatric gastroenterologist or hepatologist to adjust the corticosteroid regimen.

#### Reference:

Patients and carers, EMA, 13 January 2023 ([link to the source within \*www.ema.europa.eu\*](#))

## Opioids

### Use in patients with a history of mental health disorders

**Canada.** Health Canada has alerted health-care professionals that opioids should be used with particular care in patients with a history of mental health disorders such as major depression, anxiety and alcohol and drug abuse.

A recent analysis suggested that mood disorders often occur with opioid pain relief medication among adults. The analysis also suggested that among adults with mood disorders, opioid medication was not taken as directed or for reasons other than pain relief.

Health-care professionals are further advised that concerns

about abuse, addiction, or diversion should not prevent the proper management of pain. The benefits and risks of opioid medications based on the needs of each patient should be carefully assessed before prescribing.

**Reference:**

Health Product InfoWatch,  
Health Canada, February 2023  
([link to the source within www.hc-sc.gc.ca](#))

## Pseudoephedrine

### Risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS)

**Europe.** Following reports of the risk of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS), the PRAC has started a review of pseudoephedrine.

Pseudoephedrine is taken orally and is used for the treatment of nasal congestion resulting from a cold, flu or allergy. It has a known risk of cardiovascular and

cerebrovascular ischemic events, including stroke and heart attack. These restrictions and warnings are already included in the product information.

Small number of cases of PRES and RCVS have been reported in pharmacovigilance databases and the medical literature in people using pseudoephedrine.

The PRAC will review available evidence and decide whether the marketing authorizations for pseudoephedrine should be maintained, varied, suspended or withdrawn across the EU.

**Reference:**

Patients and carers, EMA, 10 February 2023 ([link to the source within www.ema.europa.eu](#))

## Topical testosterone

### Risk of harm to children following accidental exposure

**United Kingdom.** The Medicines and Healthcare Products Regulatory Agency (MHRA) has alerted health-care professionals that premature puberty and genital enlargement have been

reported in children who were accidentally and repeatedly exposed to an adult using topical testosterone.

Topical testosterone products are gels or creams applied directly to the skin and are used to replace testosterone in men who do not produce sufficient natural testosterone (hypogonadism).

Health-care professionals should inform patients of the potential consequences if topical testosterone is accidentally transferred to other people. Patients should be advised to wash their hands after application of topical testosterone. It is essential to cover the application site with clothing once the product has dried, and wash the application site before physical contact with another adult or child to reduce these risks.

**Reference:**

Drug Safety Update, MHRA, 25 January 2023 ([link to the source within www.gov.uk/mhra](#))

## Call for Submissions

We are very keen to make this newsletter even more useful to all our readers. We are calling out to all national medical products regulatory authorities to send us the latest information on safety and regulatory actions on medicinal products from their countries.

We also welcome short reports on any recent events or achievements in pharmacovigilance in your country.

All submissions will be reviewed for relevance and subject to the WHO internal selection, editorial review, and clearance process.

Please send your submissions or questions to: [pvsupport@who.int](mailto:pvsupport@who.int)

## **Summary and recommendations from the second joint meeting of the WHO Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP)**

14–16 December 2022

WHO convened the second joint meeting (hybrid) of the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP) from 14 to 16 December 2022.

Following the WHO transformation in 2020, in which the work related to the safety of medicines and vaccines were combined within the Regulation and Safety Unit (REG), joint meetings of the Advisory Committee on Safety of Medicinal Products (ACSoMP)<sup>1</sup> and the Global Advisory Committee on Vaccine Safety (GACVS)<sup>2</sup> were established. A summary of the presentations and recommendations from the medicines-specific sessions and from sessions of common interest for the pharmacovigilance of both medicines and vaccines is provided below<sup>3</sup>. The medicines-specific sessions were co-chaired by Dr June Raine from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and Dr Gerald Dal Pan from the United States Food and Drug Administration (USFDA) and sessions common to both vaccines and medicines were co-chaired by Dr Dure Samin Akram from the Health, Education and Literacy Program in Pakistan and Dr Gerald Dal Pan.

### **1. Update on molnupiravir active safety surveillance pilot study**

Molnupiravir was conditionally recommended in March 2022 for the treatment of mild to moderate COVID-19 infection in those at highest risk of hospitalisation. The conditional recommendation reflects the concern about its widespread use before more safety data become available, and mitigation strategies include undertaking active pharmacovigilance surveillance.<sup>4</sup> To support the WHO clinical guidelines, WHO has published a protocol for a cohort event monitoring (CEM) study and is supporting countries to implement it. CEM is an active surveillance method that can be used to follow-up early users of molnupiravir to ensure timely collection of post-marketing safety data.<sup>5</sup> The primary objective of the CEM study is to characterize and estimate the incidence of all adverse events (AEs) and serious AEs (SAEs). The secondary objectives included the characterization and estimation of the prevalence of maternal and perinatal outcomes in women inadvertently exposed to molnupiravir during pregnancy. The Pan American Health Organization (PAHO) has also adapted the protocol for use in their region. The progress of this study was presented to ACSoMP. Currently, WHO is supporting four countries to implement the study (Bangladesh, Egypt, Jordan and the Philippines). Countries are at the stage of obtaining country specific ethics approval and two countries are expecting to start data collection in the first quarter of 2023. WHO Headquarters (HQ) has developed a generic digital platform to collect data from multiple data sources with mobile and Internet tools and pool the data at a central hub at WHO. This tool will be useful for data collection in other safety surveillance studies in the future. A statistical analysis plan has been developed and WHO will update the protocol to include the safety monitoring of nirmatrelvir-ritonavir, which is also a WHO recommended COVID-19 treatment.

### **Advice and conclusions**

- ACSoMP recommended that WHO should promptly communicate the results from any interim analyses that become available to the ACSoMP Subcommittee for COVID-19 therapeutics.

<sup>1</sup> Members of ACSoMP: [https://cdn.who.int/media/docs/default-source/pvg/acsomp/acsomp-composition.pdf?sfvrsn=7c4030da\\_2](https://cdn.who.int/media/docs/default-source/pvg/acsomp/acsomp-composition.pdf?sfvrsn=7c4030da_2)

<sup>2</sup> Members of GACVS: [https://cdn.who.int/media/docs/default-source/pvg/global-vaccine-safety/current-members-feb-2021.pdf?sfvrsn=6733b419\\_24](https://cdn.who.int/media/docs/default-source/pvg/global-vaccine-safety/current-members-feb-2021.pdf?sfvrsn=6733b419_24)

<sup>3</sup> The summary of vaccine-specific sessions is published on another document: World Health Organization. 2023. Weekly Epidemiological Record, 2023, 98 (09), 83-92. Available from: <https://apps.who.int/iris/handle/10665/366342>

<sup>4</sup> World Health Organization. 2023. Therapeutics and COVID-19: Living guideline. Available from: [https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022\\_2](https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022_2), last accessed 1 March 2023.

<sup>5</sup> World Health Organization. 2022. Safety monitoring of molnupiravir for treatment of mild to moderate COVID-19 infection in low and middle-income countries using cohort event monitoring: a WHO study. Available from: <https://apps.who.int/iris/handle/10665/352394>, last accessed 1 March 2023.

### 2. Update on ocular adverse events during leishmaniasis treatment with miltefosine

Miltefosine is an oral anti-infective and one of the medicines with established efficacy in the treatment of some forms of leishmaniasis, a parasitic infection spread by sandflies. Leishmaniasis can take different forms, including cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL). Post-Kala-Azar Dermal Leishmaniasis (PKDL) is a sequela which generally occurs 6 months to several years after apparent cure of VL. It is generally prevalent in areas endemic for *L. donovani* in South Asia (Bangladesh, India and Nepal) and East Africa (mainly in Sudan). Although uncommon, leishmanial ocular infections have been reported, and keratitis and uveitis can also occur with the disease. A 12-week treatment course of miltefosine is used to treat PKDL in South Asia.

Following reports of ocular adverse events in patients treated with miltefosine, originating mostly from South-Asia, ACSoMP has previously recommended that WHO investigate this issue further. The proposed method was discussed with ACSoMP in June 2022 and WHO established a Multidisciplinary Technical Group (MTG) to advise on the causality, the risk characteristics and frequency, risk minimization measures, risk communication, remaining uncertainties and the need for further studies. To facilitate the work of the MTG, WHO, supported by the German national regulatory authority (BfArM) and the Uppsala Monitoring Centre (UMC), collected and compiled all available evidence and information on the causal relationship between reports of serious ocular events and exposure to miltefosine. The findings and recommendations from the MTG were presented to ACSoMP.

Based on the evidence, the MTG concluded that a causal relationship between ocular adverse events and the exposure to miltefosine is at least a reasonable possibility. The risk of ocular adverse events was observed mostly during the treatment of patients, both men and women, with PKDL in south Asia, including children under 18 years old, and were mostly observed beyond 28 days of treatment. No other risk factors were identified. Most, but not all, ocular events resolved after miltefosine was withdrawn or symptomatic treatment, e.g., steroids and topical antibiotics, was started.

#### **Advice and conclusions**

ACSoMP supported the recommendations from the Multidisciplinary Technical Group (MTG), including:

- the inclusion of the proposed warning and list of ocular adverse events in the summary of product characteristics and the patient information leaflet for miltefosine. All stakeholders should ensure that product information is provided in a language that is understood by local healthcare professionals and patients to enable effective risk communication;
- the additional guiding principles for the prevention, early detection and management of eye complications in patients treated with miltefosine;
- the development of a patient information brochure by WHO based on the MTG recommendations to facilitate risk communication;
- communication via a statement on WHO's website, the publication of the public assessment report and publications in peer-reviewed journals
- communication of conclusions through disease programmes and to investigators of identified ongoing clinical trials;
- in countries where it is feasible, a Direct Healthcare Professional Communication by national regulatory authorities;
- the use of active surveillance (such as a cohort event monitoring (CEM) study), supported by a follow-up questionnaire, to characterize the risk and its frequency and to assess the effectiveness of the risk minimization measure;
- Collaboration of PV programme with disease programme, to ensure efficient real time data sharing, rapid analysis and interpretation;
- implement a study analysing miltefosine pharmacokinetics, the presence of parasites and immune reactions in patients with PKDL to assess the specificity and causality of this adverse event in these patients.

### 3. Update on hallucinations reported with Delamanid in children

Delamanid has been recommended for use in treating multidrug-resistant tuberculosis (MDR-TB) or rifampicin resistant tuberculosis (RR-TB). The current WHO recommendation is that delamanid may be included in the treatment of MDR/RR-TB patients of all ages, as part of a longer regimen. (conditional recommendation. Moderate certainty of evidence for MDR/RR-TB patients aged 3 years or more; very low certainty of evidence for children with MDR/RR-TB aged below 3 years). In October 2021, ACSoMP discussed the signal of hallucinations in children treated with Delamanid and recommended that the signal should be evaluated further with a specialist in childhood psychology and sleep disorders. ACSoMP recommended that

the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (UMC) in collaboration with other relevant experts should do an in-depth investigation. The results of this investigation were presented by UMC to ACSoMP. They showed that although the term 'hallucinations', particularly 'hypnopompic hallucinations' were given in the reports, the profiles of most cases seemed to be more consistent with nightmares or night terrors, which mostly disappeared when treatment ended. It was concluded that sleep disorders are common in children and difficult to distinguish from adverse effects of medications. However, the association between sleep disorders (night terrors and nightmares) and the use of delamanid indicates a possible relationship.

### **Advice and conclusions**

- ACSoMP carefully assessed the response to this safety signal and feel that the response has been appropriate.
- Given that the product label has been modified by the market authorization holder to include hallucinations as an adverse event, and the potential of misclassifying 'night terrors' and 'nightmares', which are common in child development, as 'hallucinations', the risk mitigation actions already undertaken by the market authorization holder were considered to be sufficient and ACSoMP recommended that a 'watch and wait' strategy would be reasonable since the evidence of hallucinations in children is uncertain.

## **4. Update on dolutegravir exposure at conception and neural tube defects**

Dolutegravir (DTG) has been regularly discussed by ACSoMP in recent years. DTG is a widely used and highly effective antiretroviral medication recommended for HIV/AIDS treatment. In 2018, confidence in this medicine was shaken when preliminary results from a nationwide birth surveillance programme in Botswana found a potential association between periconceptional exposure to DTG with the development of neural tube defects (NTDs) in a setting without a folate supplementation programme. However, as the cohort of this study grew in subsequent years, the prevalence of NTD in women with periconceptional exposure to DTG was no longer significantly higher than in women without periconceptional exposure to DTG or efavirenz or any other comparison group. This refutes the initial NTD signal, as the signal was based on a relatively small number of exposures, and has since been corrected with larger number of exposures. An update of the results from studies in other settings continue to show that DTG is highly effective and safe in pregnant women and that NTDs are not more frequent following periconceptional exposure. Although DTG has been shown to be an effective HIV treatment, the initial signal seems to continue to have an impact on women's uptake in lower- and middle-income countries (LMICs) and a gap still exists between uptake by men and women.

### **Advice and conclusions**

- ACSoMP considered that the results of the studies were reassuring and need to be communicated more widely and effectively, for example, by engaging with regulators in the regions to ensure effective integration of these results in patient information leaflets;
- ACSoMP recommended that communication strategies should include actions for patients and field healthcare professionals;
- ACSoMP recommended that the lessons learnt should be used to inform strategies to improve the use of medical products and vaccines in pregnant women more broadly;
- ACSoMP requested that information on DTG use and updated data on the safety of new, long-acting antiretrovirals for HIV prevention and treatment in pregnant women continue to be reported annually to them.

## **5. Sodium valproate use in women and girls of childbearing potential: Update of WHO's Mental Health Gap (mhGAP) guidelines**

The use of sodium valproate/valproic acid-containing products in women and girls of childbearing potential has been discussed in previous ACSoMP meetings. The Committee was informed of the upcoming Mental Health Gap (mhGAP) guideline update which has recommendations for the treatment of epilepsy and bipolar disorder in addition to other mental health conditions. The Guideline development group (GDG) reviewed evidence for the effectiveness and safety of antiseizure medicines in women and girls of childbearing potential and the recommendation for the use of valproic acid in this population will be updated. The updated mhGAP guideline is expected to be published this year. Meanwhile, WHO has published an addendum to the

mhGAP Intervention Guide to reflect that valproate should not be used in women and girls of childbearing potential because of potential harm to the foetus<sup>6</sup>.

ACSoMP discussed the importance of communicating the risks of valproic acid during pregnancy and emphasized the need to make resources and tools available to improve knowledge at the country-level. There is a need to raise awareness early in women's reproductive life and to provide guidance on alternative treatments.

### **Advice and conclusions**

- ACSoMP recommended that a pre-guideline announcement, advocacy, communication and training materials should be developed urgently ahead of the publication of the revised guidelines;
- ACSoMP recommended that there is a need for communication about alternative treatments and medication switching methods;
- ACSoMP recommended that more effective and user-friendly methods for communicating this risk should be explored in LMICs.

### **6. Update on therapeutic guidelines for mpox and emergency use protocol for tecovirimat under the MEURI framework**

On 23 July 2022, WHO declared the global mpox outbreak a public health emergency of international concern after reports of mpox outbreaks in several non-endemic countries. The mpox virus is a member of the *Orthopoxvirus* genus in the **Poxviridae** family and is related to the virus that caused smallpox, that was eradicated in 1980. Tecovirimat is an antiviral that inhibits p37, a highly conserved protein in all Orthopoxviruses. In January 2022, the European Medicines Agency (EMA) authorized its use for smallpox, mpox and cowpox under exceptional circumstances, based on evidence of a reduction in mortality for these diseases in animal studies and conditional that the marketing authorization holder, SIGA, provide data on the effectiveness and safety in the event of a smallpox outbreak. In July 2022, tecovirimat was approved in the UK for smallpox, mpox, cowpox, and vaccinia complications in adults and children. The US CDC has a protocol for expanded access to allow access to and use of tecovirimat for treatment of non-variola *Orthopoxvirus* infections, including mpox, in adults and children. There are several ongoing randomized clinical trials but results will not be available until mid-2023, at the earliest. Although there is insufficient evidence to inform clinical management guidelines, WHO has developed the emergency use protocol under the MERUI (Monitored Emergency Use of Unregistered and Experimental Interventions) ethical framework to provide access to tecovirimat to patients with mpox and to characterize the clinical characteristic of the cohort receiving tecovirimat including the monitoring of any adverse or serious adverse events. WHO will convene an independent Data Monitoring Committee (DMC) to review the AEs and to report findings to national sponsors, relevant authorities and others DMCs. Serious AEs and suspected unexpected serious adverse reactions (SUSARs) will be reported via national pharmacovigilance systems to the WHO global database of individual case safety reports, VigiBase.

### **7. Update on ACSoMP Subcommittee activities on COVID-19 therapeutics**

The ACSoMP COVID-19 Subcommittee was set up in January 2022 to review, evaluate and interpret post-introduction COVID-19 medicine safety data and to advise WHO on the overall safety of COVID-19 medicines and the need for additional monitoring or risk mitigation as well as the communication strategy of the safety data. The Subcommittee has held eight meetings since it was set up and has reviewed available postmarketing safety data for baricitinib, molnupiravir, nirveltrami-ritonavir, sotrovimab, and tocilizumab.

### **Advice and conclusions**

- ACSoMP recommended improving methods to detect safety signals in LMICs and that the safety of a wider variety of products, particularly those used in LMICs should be assessed.

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<sup>6</sup> World Health Organization. 2023. mhGAP-Intervention Guide (mhGAP-IG 2.0) Addendum on the use of valproic acid (sodium valproate) in women and girls of childbearing potential, January 2023, [https://cdn.who.int/media/docs/default-source/brain-health/mhgap\\_ig\\_v4\\_0\(08032022\).pdf?sfvrsn=696f27df\\_21](https://cdn.who.int/media/docs/default-source/brain-health/mhgap_ig_v4_0(08032022).pdf?sfvrsn=696f27df_21)

### **8. Update on monitoring safety during pregnancy and breastfeeding projects: Pregnancy Exposure Registries Landscape Analysis (PERLA) and the COVID-19 pregnancy cohort study**

Monitoring safety in pregnancy was discussed in the previous joint ACSoMP and GACVS meeting. An update on the progress of the Pregnancy Exposure Registries Landscape Analysis (PERLA) was provided. This project is a collaboration between the WHO Pharmacovigilance team and PATH (formerly known as the Programme for Appropriate Technology in Health). The project aims to identify registries, databases, surveys and other sources in LMICs that record exposure to drug and vaccine products during pregnancy and the subsequent maternal and perinatal outcomes. A literature search, a key informant survey and interviews were used to gather information. A report will be finalized in the first quarter of 2023 and results will be submitted for publication in the second or third quarter of 2023.

An update on the WHO COVID-19 pregnancy cohort study was also provided, this longitudinal study was developed early in the COVID-19 pandemic and captures information on maternal, pregnancy, perinatal, neonatal and postpartum outcomes in pregnant women.<sup>7</sup> In the November 2022 updated protocol vaccine-related outcomes, data collection forms and analyses were added. The study is being conducted in eight countries in five WHO regions. Enrolment started in June 2021 and is expected to terminate in the second quarter of 2023. The enrolled women are followed every 4–6 weeks and up to 6 weeks postpartum and the neonates are followed for 4 weeks postpartum. The study will assess COVID-19 vaccine uptake during pregnancy, describe symptoms and non-pregnancy-related events after vaccination during pregnancy and if feasible, determine if the risk of adverse outcomes differs in pregnant women who received COVID-19 vaccine during pregnancy and those who did not.

As of 2 December 2022, 15 538 pregnant women and 8143 vaccinated pregnant women had been enrolled. Over 60% of the vaccinated pregnant women have received non-mRNA vaccines. Some limitations to the study design include the difficulty of studying rare outcomes and signals, although data can be pooled across countries to increase the statistical power to detect rarer events. In addition, the study is labour-, time- and resource-intensive. The infrastructure that has been established will be available for future studies of other exposures of pregnant women.

#### **Advice and conclusions**

- ACSoMP and GACVS suggested that it would be very useful to maintain the infrastructure of the study to enable maternal and neonatal data to be collected routinely, although they recognized there could be challenges, such as resources.

### **9. Serious games approach to risk and safety communication strategies: 'The Good Talk!'**

The serious games approach was discussed as a potential risk communication strategy for pharmacovigilance. Serious games are designed to be interactive, fun and entertaining (motivating) while they educate, train or change users' (i.e., players') behaviour, while addressing issues such as vaccine hesitancy and misunderstanding of adverse events and mistrust. 'The Good Talk!' is an application based on the serious games approach to increase the skills of vaccine advocates to enable them to have open conversations about COVID-19 vaccination with their close contacts who are vaccine hesitant. Once the game has been finalized, a low-bandwidth deployment package will be available that can be adapted to local contexts by changing the graphics, the text and names, while the underlying method remains the same. An evaluation protocol to determine how effective the tool is in terms of changing people's behaviour in each new setting will be included in the deployment package.

Declaration of interests; All members of Advisory committees are requested to fill in a declaration of interest form prior to each meeting. All experts were cleared in having no conflicts declared, or when declared, assessed as nonconflicting.

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<sup>7</sup> World Health Organization. 2022. Generic protocol: a prospective cohort study investigating maternal, pregnancy and neonatal outcomes for women and neonates infected with SARS-CoV-2, 1 November 2022, version 3.1. Available from: <https://www.who.int/publications/i/item/WHO-2019-nCoV-pregnancy-and-neonates-2022.1>, last accessed 1 March 2023.

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