



World Health
Organization

WHO Pharmaceuticals **NEWSLETTER**

2023

No. **4**

**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:*

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*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 the conclusions from the meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held from 11 to 12 May 2023.

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WHO Pharmaceuticals Newsletter No. 4, 2023

ISBN 978-92-4-008265-6 (electronic version)

ISBN 978-92-4-008266-3 (print version)

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Crizanlizumab

Revocation of marketing authorization

Europe. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) has recommended revoking the marketing authorization for crizanlizumab (Adakveo®) because the benefits of the medicine did not outweigh its risks. This recommendation has been followed by a legally binding decision by the European Commission.

Crizanlizumab is indicated for the prevention of vaso-occlusive crises (painful crises when the microcirculation is obstructed by sickled red blood cells) in patients aged 16 years and older with sickle cell disease.

The CHMP reviewed the results of the STAND study (Study of two doses of crizanlizumab versus placebo in adolescent and adult sickle cell disease patients), which showed that crizanlizumab did not reduce the number of painful crises leading to a healthcare visit over the first year of treatment (on average 2.5 painful crises in the crizanlizumab group compared with 2.3 crises in the placebo group). In terms of safety, the STAND study did not raise new concerns but showed a higher rate of severe and serious treatment-related adverse events for crizanlizumab compared with placebo. The CHMP concluded that its benefits do not outweigh the risks.

Health-care professionals should not start any new patients on crizanlizumab. This should be explained to patients

currently on treatment with crizanlizumab and alternative treatments discussed.

Reference:

Patients and carers, EMA, 26 May and 3 August 2023 ([link1](#), [link2](#) to the source within www.ema.europa.eu)

Diazoxide

Potential risk of necrotizing enterocolitis

Canada. Health Canada has announced that the product information for diazoxide (Proglycem®) is to be updated to include the potential risk of necrotizing enterocolitis (inflammation and death of tissue in the small or large intestine) of a newborn or infant.

Diazoxide is indicated for the management of hypoglycaemia in infants, children and adults caused by hyperinsulinism, when other medical therapy or surgical management has been unsuccessful or is not feasible.

Triggered by cases published in the scientific literature, Health Canada reviewed information from the Canada Vigilance database. Health Canada reviewed 21 cases (one domestic and 20 international), of which 15 (all international) met the criteria for further assessment. All 15 cases assessed were reported in infants two months of age or younger, with 13 of the 15 cases occurring within the first 28 days of life. Of the 15 cases, two were found to be probably linked to the use of diazoxide, 11 were found to be possibly linked (three deaths included), one was unlikely to be linked and one could not be assessed. The review found a possible link between the use

of diazoxide and the risk of necrotizing enterocolitis in newborns and infants.

Reference:

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

D-norpseudoephedrine

Withdrawal of marketing authorization

Mexico. The Federal Commission for Protection against Health Risks (COFEPRIS) has revoked the marketing authorization for two weight-loss products containing D-norpseudoephedrine (Redotex®, Redotex NF®).

The COFEPRIS identified and reviewed 837 reports of adverse events associated with the consumption of those medicines, where various adverse events including heart and pulmonary disorders, as well as anxiety and insomnia were reported.

Health-care professionals are recommended to avoid prescribing the medicines and any other product containing D-norpseudoephedrine, as well as to consider other therapeutic alternatives for obesity patients.

Reference:

Press release, COFEPRIS, 18 May 2023 ([link](#) to the source within www.gob.mx/cofepris)

Febuxostat

Updated advice for treatment of patients with a history of major cardiovascular disease

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated the advice in the product information of febuxostat so that febuxostat is used cautiously in patients with pre-existing major cardiovascular diseases, particularly in those with evidence of high urate crystal and tophi burden or those initiating urate-lowering therapy. Prescribing clinicians should titrate febuxostat appropriately to minimize gout flares following initiation.

Febuxostat is indicated for the treatment of chronic hyperuricaemia (gout) and the prevention and treatment of hyperuricaemia in patients undergoing chemotherapy. In 2019, the MHRA advised health-care professionals to avoid febuxostat treatment in chronic hyperuricaemia patients with pre-existing major cardiovascular diseases, unless no other therapy options were appropriate, based on the risk identified from the CARES study (Cardiovascular safety of febuxostat and allopurinol in participants with gout and cardiovascular comorbidities).

Additionally, MHRA has reviewed the results from a further trial on the cardiovascular safety of febuxostat, the FAST study (Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout), which concluded that febuxostat was non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and, unlike the CARES study results, that long-term use was not associated with an increased risk of death or cardiovascular death compared to allopurinol. Based on the review, the product information retains the warning

for cardiovascular disorders and now advises that treatment of patients with pre-existing major cardiovascular diseases with febuxostat should be exercised cautiously.

Reference:

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

(See also WHO Pharmaceuticals Newsletter [No.5, 2019](#): Febuxostat and Increased risk of cardiovascular death and all-cause mortality in Ireland)

Mercaptopurine

Potential risk of hypoglycaemia

Canada. Health Canada has announced that the product safety information for mercaptopurine is to be updated to include the potential risk of hypoglycaemia (low blood sugar) in children less than 18 years of age.

Mercaptopurine is indicated for the maintenance therapy for a specific type of cancer of the blood and bone marrow (acute lymphoblastic, lymphocytic leukaemia) in combination with other medicines in adults and children.

Prompted by a USFDA update to the product information to include the risk of hypoglycaemia in children, as well as Canadian and international cases reported, Health Canada reviewed information provided by the manufacturer, and from the Canada Vigilance and published literature. Health Canada reviewed 23 cases (one domestic, 22 international), of which 22 cases were reported in children under 18 years of age and 12 cases were in children under six years of age. Of the 23 cases, six were found

to be probably linked to the use of mercaptopurine, 15 (one domestic) were found to be possibly linked and two were unlikely to be linked. The review concluded that there may be a link between the use of mercaptopurine and the potential risk of hypoglycaemia in children.

Reference:

Health Product InfoWatch, Health Canada, June 2023 ([link](https://www.hc-sc.gc.ca) to the source within www.hc-sc.gc.ca)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Potential risks following prolonged use after 20 weeks of pregnancy

United Kingdom. The MHRA has announced that the product information for non-steroidal anti-inflammatory drugs (NSAIDs) has been updated to include the risk of oligohydramnios (low levels of amniotic fluid surrounding the baby) and premature closure of the ductus arteriosus (narrowing of a connecting blood vessel in the baby's heart) in the second trimester of pregnancy. It now includes advice to avoid use from week 20 of pregnancy onwards unless considered necessary by a clinician.

A review of data from a 2022 study has newly identified that prolonged use of NSAIDs from week 20 of pregnancy onwards may be associated with an increased risk of oligohydramnios and foetal renal dysfunction. Some cases of constriction of the ductus arteriosus have also been identified at this early stage.

The advice in this article applies to oral NSAIDs and NSAIDs administered by injection (available on prescription). As a reminder, use of systemic (oral and injectable) NSAIDs such as ibuprofen, naproxen, and diclofenac are contraindicated in the last trimester of pregnancy (after 28 weeks of pregnancy).

If, following consultation between the patient and a health-care professional, use of a systemic NSAID after week 20 of pregnancy is considered necessary, it should be prescribed for the lowest dose for the shortest time and additional neonatal monitoring considered if used for longer than several days.

Reference:

Drug Safety Update, MHRA, 27 June 2023 ([link to the source within \[www.gov.uk/mhra\]\(http://www.gov.uk/mhra\)](#))
(See also WHO Pharmaceuticals Newsletter [No. 4, 2022](#): Risks of maternal, foetal and neonatal adverse effects in pregnancy in New Zealand)

Oral anticoagulants

Potential risk of anticoagulant-related nephropathy (ARN)

Australia. The Therapeutic Goods Administration (TGA) has announced that the product information for all oral anticoagulants has been updated to include the potential risk of anticoagulant-related nephropathy (ARN). This is a rare but serious adverse event resulting from profuse glomerular bleeding. It has the potential to cause irreversible kidney damage and death. Although rare, ARN is likely to be underdiagnosed as a cause of acute kidney injury.

Oral anticoagulants include factor Xa inhibitors - apixaban (Eliquis®) and rivaroxaban (Xarelto®), direct thrombin inhibitors - dabigatran (Pradaxa®), vitamin K antagonists - warfarin (Coumadin®, Marevan®) in this class of medicines. They are indicated for the prevention and treatment of thromboembolic conditions.

The TGA investigated a safety signal of reports of ARN in patients taking oral anticoagulants and sought expert advice from the Advisory Committee on Medicines (ACM) that reported it was well documented in the medical literature with warfarin and other oral anticoagulants. The ACM supported the class-wide warning due to the wide use of the medicines and seriousness of this adverse event. The ACM did not consider a warning for parenteral anticoagulants currently because they are mainly used in hospitals and for a shorter duration.

Health-care professionals are advised that acute kidney injury may occur in patients with altered glomerular integrity or with a history of kidney disease, possibly in relation to episodes of excessive anticoagulation and haematuria or even without pre-existing kidney disease. Close monitoring including renal function evaluation is advised in patients with excessive anticoagulation, compromised renal function and haematuria (including microscopic).

Reference:

Safety updates, TGA, 1 June 2023 ([link to the source within \[www.tga.gov.au\]\(http://www.tga.gov.au\)](#))

Pegaspargase

Risk of hypersensitivity reactions

Pakistan. The National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) has announced that the product information for pegaspargase should be updated to include the risk of hypersensitivity reaction.

Pegaspargase is indicated for the treatment of acute lymphoid leukaemia in paediatric and adult patients who have hypersensitivity to the native forms of L-asparaginase.

The NPC-DRAP reviewed six case reports of hypersensitivity reactions with pegaspargase injection used in children with acute lymphoid leukaemia occurring within one day of the administration. All cases were evaluated as having a possible relationship between the medicine and events. The Pharmacovigilance Risk Assessment Expert Committee decided to update the product information to include the risk of hypersensitivity reaction together with the advice on monitoring and treatment modification as per the grade of hypersensitivity reaction.

Patients are advised to talk with their doctors if they have a history of hypersensitivity to conventional asparaginase formulations. Health-care professionals are advised of the needs for pre-medication 30-60 minutes before administration of pegaspargase followed by post-monitoring for an hour. Discontinuation of the

treatment is recommended for serious reactions and modification of the treatment is advised based on the severity of the reaction.

Reference:

Drug Safety Alert, DRAP, 11 April 2023 ([link to the source within https://www.dra.gov.pk](https://www.dra.gov.pk))

Prescription stimulants

Risk of misuse and abuse in people who get the medicines outside prescription

United States. The US Food and Drug Administration (FDA) is requiring updates to the prescribing information of prescription stimulants to consistently include warnings about the harms of misuse and abuse, and alerting that such users get their medicines from family members or peers.

Prescription stimulants (e.g., amphetamine, dextro-amphetamine, methylphenidate) are used to treat attention deficit/hyperactivity disorder (ADHD), binge-eating disorder, and uncontrollable episodes of deep sleep called narcolepsy.

Health-care professionals should regularly assess and monitor patients throughout treatment for signs and symptoms of nonmedical use, addiction, and potential diversion, evidenced by frequent renewal requests and higher dose than warranted. Patients should be informed that sharing these medicines with others can lead to development of substance use disorder and addiction in those with whom these medicines are shared.

Reference:

FDA News Release, US FDA, 26 May 2023 ([link to the source within www.fda.gov](https://www.fda.gov))

Renin-angiotensin system inhibitors

Strengthened warning on use in women of child-bearing potential

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for renin-angiotensin system (RAS) inhibitors will be updated to strengthen warning on the use in women of child-bearing potential.

RAS inhibitors, including angiotensin-converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor blockers (ARBs), an angiotensin receptor-neprilysin inhibitor, and a direct renin inhibitor, are indicated for the treatment of hypertension and chronic heart failure. RAS inhibitors are contraindicated in pregnant women or women who may be pregnant due to the risk on foetus including oligohydramnios, foetal or neonatal death, or neonatal hypotension, renal failure, hyperkalaemia, and skull hypoplasia.

In 2014, PMDA alerted health-care professionals of the risk of administering these medicines to pregnant women following several case reports where patients were continuously treated with ACE inhibitors or ARBs even after their pregnancy was detected, and the reported adverse events in

foetuses were possibly associated with the maternal use of those medicines. However, even after the alert, similar cases have been reported including in women without recognizing that they were pregnant. The MHLW and the PMDA requested to add the following precautions for the administration of RAS inhibitors to women of child-bearing potential:

- Women of child-bearing potential should be administered RAS inhibitors only if the potential therapeutic benefits are considered to outweigh the potential risks.
- If to be administered, absence of pregnancy should be confirmed prior to and during the administration periodically. If pregnancy is detected, the administration should be discontinued immediately.
- Patients should consult the physician if pregnancy is planned, and immediately if pregnancy is detected or suspected.

Reference:

Safety Information, MHLW/PMDA, 30 May 2023 ([link to the source within www.pmda.go.jp/english/](https://www.pmda.go.jp/english/))

Sulfamethoxazole, trimethoprim

Risk of haemophagocytic lymphohistiocytosis (HLH)

Canada. Health Canada has announced that the product safety information for combination sulfamethoxazole and trimethoprim-containing products will be updated to include the risk of haemophagocytic

lymphohistiocytosis (HLH). HLH is a condition where large numbers of white blood cells build up in, and damage organs and destroy other blood cells.

Combination sulfamethoxazole and trimethoprim is a prescription antibiotic medicine indicated for the treatment of various bacterial infections, such as urinary tract infections, respiratory tract infections, and gastrointestinal infections.

Triggered by a labelling update for these products by the EMA, Health Canada reviewed the available information from the Canadian and international databases. Of the ten cases assessed, one case was found to be probably linked to the use of the medicine, eight were found to be possibly linked (including one fatal case) and one (another fatal case) was unlikely to be linked. The review found a possible link between the use of the medicine and the risk of HLH.

Reference:

Health Product InfoWatch, Health Canada, June 2023 ([link to the source within www.hc-sc.gc.ca](https://www.hc-sc.gc.ca))

Topiramate

Risk of neurodevelopmental disorders in children exposed in-utero

1. New Zealand. The Medsafe has announced that the product information for topiramate (Topamax®) is updated to include the risk of neurodevelopmental disorders and birth defects in children whose mothers were taking topiramate during pregnancy.

Topiramate is a medicine used to treat epilepsy in adults and children aged two years and

older. It is also indicated in adults for the prevention of migraines. Its product information already includes information about the risk of congenital malformations.

The risk of neurodevelopmental disorders was noted in an observational study based on data from five Nordic pregnancy registries. The registries captured information from over 24,000 children exposed to at least one antiepileptic medicine before birth. Of these children, 471 were exposed to topiramate alone. The authors reported a 2.77-fold increase in the risk of autism spectrum disorder and a 3.47-fold increase in the risk of intellectual disability in children with an epileptic mother taking topiramate during pregnancy compared to those with epileptic mothers not taking any antiepileptic treatment during pregnancy.

Health-care professionals are advised that topiramate should only be used to treat epilepsy in pregnancy if the potential benefit justifies the potential risk to the mother and foetus. Pregnancy testing should be performed before starting treatment, and women of childbearing potential should use a highly effective contraceptive method during treatment. The use of topiramate for migraine prophylaxis is contraindicated in pregnancy.

Reference:

Safety Communications, Medsafe, 11 April 2023 ([link to the source within www.medsafe.govt.nz](https://www.medsafe.govt.nz))

2. Australia. The TGA has announced that the product information for topiramate (Topamax®) is updated to

include the risk of foetal neurodevelopment disorder, updated warning about women of childbearing potential, and contraindications in pregnancy and women of childbearing potential for migraine prophylaxis.

Reference:

Safety updates, TGA, 23 June 2023 ([link to the source within www.tga.gov.au](https://www.tga.gov.au))

(See also WHO Pharmaceuticals Newsletter [No.3, 2022](#): Topiramate and Potential risk of neurodevelopmental disorders in children exposed in-utero in Europe)

Tramadol

Risks of sleep-related breathing disorders, adrenal insufficiency and serotonin syndrome

Ireland. The Health Products Regulatory Authority (HPRA) has announced that the product information for tramadol has been updated to include the risks of sleep-related breathing disorders and adrenal insufficiency, as well as an update to the information on serotonin syndrome.

Tramadol is a centrally acting synthetic opioid analgesic indicated for the treatment of moderate to severe pain.

Following a review of available data, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended updates to warnings and precautions as follows:

- Tramadol can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. The risk of CSA increases in a dose-

dependent fashion.

- Tramadol may occasionally cause reversible adrenal insufficiency, requiring monitoring and glucocorticoid replacement therapy.
- Serotonin syndrome has been reported in patients receiving tramadol alone or in combination with other serotonergic agents.

Reference:

Drug Safety Newsletter, HPRA,
9 June 2023 ([link](#) to the source
within www.hpra.ie)

Zinc acetate

Risk of gastric ulcer

Japan. The MHLW and the PMDA have announced that the product information for zinc acetate will be updated to include the risk of gastric ulcer.

Zinc acetate is indicated for the treatment of Wilson's disease and hypozincaemia.

The MHLW and the PMDA assessed a total of 13 reported cases involving zinc acetate and peptic ulcer, and in the seven cases a causal relationship between the medicine and event was reasonably possible. Based on the sites of ulceration in the reports, gastric ulcer, rather than peptic ulcer, was considered as more appropriate term for precaution and added in the product information as clinically significant adverse reaction.

Reference:

Safety Information,
MHLW/PMDA, 30 May 2023 ([link](#)
to the source within
www.pmda.go.jp/english/)

Aflibercept

Risks of endophthalmitis and vitreous detachment

Egypt. The Egyptian Pharmacovigilance Center (EPVC), Egyptian Drug Authority (EDA) has alerted health-care professionals on the risks of endophthalmitis and vitreous detachment following the administration of aflibercept.

Aflibercept is a recombinant fusion for vascular endothelial growth factor-A (VEGF-A) and placental growth factor (PLGF) and is indicated for the treatment of age-related wet macular degeneration and diabetic macular oedema and retinopathy.

The EPVC received eight individual case safety reports (ICSRs) involving endophthalmitis and/or vitreous detachment after receiving aflibercept intravitreal injection.

Health-care professionals are advised about the prevention methods including aseptic technique and patient monitoring. Key signs and symptoms of intravitreal injection related adverse events include endophthalmitis, intraocular inflammation, increased intraocular pressure, retinal pigment epithelial tear and cataract.

Reference:

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

Azithromycin

Risk of fatal heart rhythms

Zimbabwe. The Medicines

Control Authority of Zimbabwe (MCAZ) has alerted health-care professionals on the risk of fatal heart rhythms with azithromycin.

Azithromycin is a macrolide antibiotic and is indicated for the treatment of various infectious diseases. The product information contains information on the risks of QT interval prolongation and torsades de pointes as well as the results of a clinical QT study which showed that azithromycin can prolong the QTc interval.

Health-care professionals should consider the risk of fatal heart rhythms with azithromycin when considering treatment options for patients who are already at risk of cardiovascular events.

Alternative medicines in the macrolide class, or non-macrolides such as fluoroquinolones, also have the potential risks of QT prolongation or other significant adverse events that should be considered.

Reference:

Medicine Information Bulletin, MCAZ, April 2023 ([link to the source within www.mcaz.co.zw](http://www.mcaz.co.zw))

Calcium chloride and calcium gluconate

Medication error leading to underdosing of calcium

United Kingdom. The MHRA has alerted health-care professionals on the risk of medication error caused by miscalculating the calcium dose administered when using calcium chloride and calcium gluconate when treating hyperkalaemia.

Both calcium chloride and calcium gluconate are used to stabilize the myocardium and prevent cardiac arrest in the treatment of severe hyperkalaemia. These two products are not dose-equivalent: 30ml of calcium gluconate 10% provides 6.8mmol of calcium. This is equivalent to 10ml of calcium chloride 10%.

The MHRA has reviewed UK data related to inappropriate use of calcium gluconate and identified isolated cases where medication errors (including one death) have occurred where 10ml of calcium gluconate was used during cardiopulmonary resuscitation. Another set of reports from the National Reporting Learning System indicated that six incidents showed incorrect calcium gluconate administration and monitoring in the context of severe hyperkalaemia and cardiac arrest (five fatal, one unknown outcome).

Health-care professionals should be alert to the risk of inadvertent underdosing if calcium gluconate is used instead of calcium chloride and verify the calcium salt content before administration.

Reference:

Drug Safety Update, MHRA, 27 June 2023 ([link to the source within www.gov.uk/mhra](http://www.gov.uk/mhra))

Fluoroquinolone antibiotics

Reminder of risk of long-lasting, disabling and potentially irreversible adverse reactions

Europe. The PRAC of the EMA is reminding health-care professionals by issuing a

Direct Healthcare Professional Communication (DHPC) that the use of fluoroquinolone antibiotics, given by mouth, injection or inhalation, is restricted due to the risk of disabling, long-lasting and potentially irreversible adverse reactions affecting several, sometimes multiple, systems, organ classes and sense.

Fluoroquinolone medicines are a family of broad-spectrum antibiotics including iprofloxacin, flumequine, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, pefloxacin, prulifloxacin and rufloxacin. They are used to treat certain types of serious infections when other antibiotics are not suitable.

Restrictions on the use of fluoroquinolone antibiotics, introduced in 2019 following an EU-wide review of these very rare but serious adverse reactions, mean that they should not be used to treat infections that might get better without treatment or by other recommended antibacterial medicines, or to prevent traveller's diarrhoea or recurring lower urinary tract infections. Importantly, fluoroquinolones should be avoided in patients who have previously had serious adverse reactions with a fluoroquinolone or quinolone antibiotic. They should be used with special caution in the elderly, patients with kidney disease and in those who have had an organ transplantation. Combined use with corticosteroid should be avoided.

[A study](#), which evaluated data from the primary care setting in six European countries

between 2016 and 2021, suggests that the measures taken to restrict the use of these medicines as a result of the EU-wide review had a modest impact. Although the use of fluoroquinolone antibiotics has reduced, these medicines may still be prescribed outside of their recommended uses.

Reference:

Patients and carers, EMA, 12 May 2023 ([link](#) to the source within www.ema.europa.eu)
(See WHO Pharmaceuticals Newsletter [No.6, 2018](#): Risk of long-lasting and disabling effects in Europe)

Glucose solutions

Medication error: accidental use instead of saline solutions in arterial lines

United Kingdom. The MHRA has reminded health-care professionals of the risk of medication error of accidentally using glucose solutions instead of saline solutions as flush fluid for arterial lines, which may contaminate blood samples and result in falsely high glucose readings. This may lead to inappropriate insulin administration and subsequent hypoglycaemia.

Flush fluids are used to maintain the patency of arterial lines when used for the continuous monitoring of blood pressure. The selection and attachment of the wrong flush fluids to arterial lines is a recognized risk, and incidents of serious clinical harm have occurred as a result. Discarding dead volume fluid is not sufficient to prevent blood contamination following the use of glucose in the flushing system.

Health-care professionals should use saline solutions (0.9% sodium chloride) to flush arterial lines and use pressure infusion bags with transparent windows to ensure that the fluid label is always visible.

Reference:

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

Hydroxyprogesterone

Potential risk of cancer in people exposed in the womb and lack of effectiveness

Europe. The PRAC of the EMA is reviewing medicines containing hydroxyprogesterone following concerns about the safety and effectiveness of these medicines.

In the EU, these medicines are available as hydroxyprogesterone caproate and are given as injections to prevent pregnancy loss or premature birth in pregnant women and for treatment of various gynaecological disorders, including disorders caused by the lack of progesterone.

The review has been initiated following a study showing that people who were exposed to hydroxyprogesterone caproate in the womb may have an increased risk of any cancer particularly when the medicine was used during the first trimester of pregnancy and with increasing dosage. Its use in the second or third trimester appeared to further increase the risk of cancer in the offspring for males but not for females. Also results from a second study (PROLONG Study) suggested that

hydroxyprogesterone caproate is no more effective than placebo in preventing recurrent premature birth or medical complications due to prematurity in the newborn infant.

EMA will communicate PRAC's recommendations once the review has concluded.

Reference:

Patients and carers, EMA, 12 May 2023 ([link1](#) and [link2](#) to the source within www.ema.europa.eu)

Oral anticoagulants

1. Reminder of dose adjustments in patients with renal impairment

United Kingdom. The MHRA has reminded health-care professionals of the current advice to ensure that all patients with renal impairment receive an appropriate dose of direct-acting oral anticoagulants (DOACs) medicines due to the increased risk of bleeding.

DOACs include apixaban, dabigatran, edoxaban, and rivaroxaban.

Exposure to DOACs is increased in patients with renal impairment and it is therefore important that patients receive an appropriate dose adjusted for renal function. Renal function in adults should be assessed by calculating creatinine clearance. Patients with renal impairment should be reviewed regularly to ensure ongoing efficacy and safety, with dosing adjusted as required. For paediatric use of these medicines, health-care professionals should counsel parents and caregivers about the reconstitution and dosing of dabigatran granules and

rivaroxaban granules to reduce the risk of medication errors.

Reference:

Drug Safety Update, MHRA, 25 May 2023 ([link](#) to the source within www.gov.uk/mhra)
(See also WHO Pharmaceuticals Newsletter [No.4, 2020](#): Direct-acting oral anticoagulants (DOACs) and Risk of bleeding in UK)

2. Ongoing assessment of abnormal uterine bleeding

New Zealand. The Medsafe is reviewing the risk of abnormal uterine bleeding (changes to normal menstrual periods) in individuals using oral anticoagulant medicines.

The Centre for Adverse Reactions Monitoring (CARM) received four reports relating to abnormal uterine bleeding with rivaroxaban during monitoring period. No reports were received for apixaban, dabigatran or warfarin.

Currently the data sheets for oral anticoagulants list bleeding and/or urogenital. To increase awareness about this adverse reaction, the Medsafe will issue an article about oral anticoagulants and abnormal uterine bleeding. The benefit risk balance for oral anticoagulants (apixaban, rivaroxaban, dabigatran, and warfarin) remains positive.

Reference:

Safety Communications, Medsafe, 27 March 2023 ([link](#) to the source within www.medsafe.govt.nz)

Valproate

New study on potential risk of neurodevelopmental disorders (NDDs) in children

after paternal exposure

1. Europe. The PRAC of the EMA is reviewing data on the potential risk of neurodevelopmental disorders (NDDs) in children conceived when fathers were taking valproate at the time of conception.

The review is focussing on data from a retrospective observational study conducted by companies using multiple registry databases in Denmark, Norway and Sweden. Initial results of the study may indicate an increased risk of NDDs in children born to men taking valproate up to three months before conception.

However, the PRAC has identified important limitations with the data from the study. In particular, the PRAC had questions about the definition of NDDs used in the study and the specific type of epilepsy the patients had. The latter is important because valproate may be prescribed more often for some types of epilepsy which are associated with NDDs.

In addition, the companies informed the PRAC about errors in the Norwegian database; the impact of these errors is not yet known.

The PRAC has therefore requested companies to provide analyses of corrected data and will review the required data as they become available.

Male patients being treated with valproate should not stop taking their medicine without consulting their doctor, as their epilepsy or bipolar disorder could become worse. Patients who have any questions about

their treatment should seek advice from their health-care professional.

Reference:

Press release, EMA, 16 August 2023 ([link to the source within www.ema.europa.eu](#))

2. United Kingdom. The MHRA has announced that it has been informed by Sanofi (MAH of Epilim®) of errors that may impact the results of study on outcomes in children whose fathers took valproate at the time of conception. As a result, the researchers from the original study are conducting a full re-analysis before any final conclusions can be drawn.

The Commission on Human Medicines (CHM) has advised that further guidance in respect of risks in children of men taking valproate should be based upon data that are accurate and complete. As soon as the revised study analysis is available, it will be re-assessed by the MHRA.

The MHRA advice that no action is currently needed for patients, and that no one should stop taking valproate without advice from their health-care professional.

Reference:

News and communications, MHRA, 16 August 2023 ([link to the source within www.gov.uk/mhra](#))

3. Singapore. The Health Sciences Authority (HSA) has announced that a Dear Healthcare Professional Letter (DHCPL) has been issued to inform health-care professionals of new safety information regarding a higher risk of NDDs in children after paternal exposure to valproate as compared to lamotrigine or levetiracetam.

Health-care professionals are advised to inform male patients of this potential risk and consider alternative therapeutic options with the patients. In men initiating or remaining on valproate treatment, it is recommended for health-care professionals to discuss with the patient the need for effective contraception.

Reference:

Announcements, HSA, 20 March 2023 ([link to the source within www.hsa.gov.sg](#))

4. New Zealand. The Medsafe has announced that the product information for valproate has been updated to include the potential risk of

NDDs in children whose fathers were treated with valproate at the time of the child's conception.

Health-care professionals are advised to inform patients of this potential risk and consider alternative treatment options for those wishing to father a child and discuss the need for effective contraception when starting sodium valproate and periodically throughout treatment.

Reference:

Safety Communications, Medsafe, 30 May 2023 ([link to the source within www.medsafe.govt.nz](#))

(See also Feature of this issue (page 16-): summary of ACSOMP meeting on 12 May 2023, WHO Pharmaceuticals Newsletter [No.2, 2023](#): summary of ACSOMP meeting on 14 December 2022, and [No.1, 2023](#): Valproate and risks in pregnancy and potential risks in male patients in UK)

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

Conclusions from the meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), 11–12 May 2023

The World Health Organization (WHO)'s Advisory Committee on Safety of Medicinal Products (ACSoMP)¹ is an independent expert advisory body established in 2003 that provides independent, authoritative scientific advice on pharmacovigilance policies and issues related to the safety of medicines to the Director General of WHO and its Member States.

WHO convened a hybrid meeting of ACSoMP from 11 to 12 May 2023, with some members joining in person in Geneva, and others joining online. The 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 (US FDA). A summary of the presentations and recommendations from the meeting is provided below.

Cohort event monitoring (CEM) for safety surveillance of molnupiravir and nirmatrelvir/ritonavir

Molnupiravir and nirmatrelvir-ritonavir have recently been authorized for the treatment of non-severe COVID-19 disease. However, there are limited data on their safety, particularly in low- and middle-income countries (LMICs). The WHO living guideline published in July 2022 made a conditional recommendation for molnupiravir and a strong recommendation for nirmatrelvir/ritonavir in patients with non-severe COVID-19 disease with the highest risk of hospitalization² and recommended the implementation of a robust active surveillance programme because of safety data gaps and concerns.

WHO has developed a protocol for cohort event monitoring (CEM)³, to support the active surveillance of molnupiravir. This protocol has been updated to include nirmatrelvir/ritonavir. The primary objectives are to characterize and estimate the incidence of all adverse events (AEs), including serious AEs, medication errors, off-label use, and misuse.

WHO has also developed digital tools for data collection in CEM. The tools and applications feature such as alerts for missed follow-up visits, availability of different access levels for different roles (site staff, principal investigators, and administrators), and automatic emails to improve follow-up of patients and events. Data can be collected from different sources, with different frequencies, formats, and structures. The tools are available in an integrated platform. The platform is customizable for use in the surveillance of both medicines and vaccines and is available as an open-source resource with an open code.

The countries implementing CEM have adapted the platform to their specific settings. The next steps include rollout of the platform, and other functionalities will be included based on user feedback.

Updates on the progress of CEM of COVID-19 therapeutics:

- In Jordan, CEM was initiated in March 2023 in six sites. However, molnupiravir has not been administered yet and nirmatrelvir-ritonavir is only available at three sites.
- In Egypt, CEM will be carried out in 10 sites once national security approval is obtained. WHO electronic tools will be used for data collection. Two variables have been added to the protocol to improve traceability: the marketing authorization holder (MAH) and the drug batch number, as there are 24 registered generic molnupiravir products.
- In the Philippines, molnupiravir is a prescription-only medication, available in pharmacies and hospitals. CEM, which will be conducted in collaboration with the Philippine College of Physicians in 25 hospitals, has just received approval from the ethics committee. Data will be collected using WHO electronic tools and paper-based diaries.

¹ Composition, Terms of Reference, and past recommendations of ACSoMP are published on: <https://www.who.int/groups/ACSoMP>

² WHO *Therapeutics and COVID-19: living guideline* [website]. Geneva: World Health Organization <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.4> (version 13, published 13 January 2023)

³ WHO 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. https://www.who.int/publications/i/item/WHO-2019-nCoV-Therapeutics-safety_monitoring-molnupiravir-2022.1

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- In Bangladesh, there are 10 registered molnupiravir products available in pharmacies and hospitals without prescription. CEM will be conducted in 10 to 15 hospitals and will be run by a Clinical Research Organization (CRO). Data will be collected using the WHO electronic tools and on paper.
- In the Pan American Region, the CEM protocol has been adapted to produce two protocols tailored to the specific safety issues associated with molnupiravir and with nirmatrelvir-ritonavir. Both CEMs aim to minimize risks by promoting the rational use of these medicines, advising against the use of molnupiravir during pregnancy and highlighting the potential for drug-drug interactions with nirmatrelvir-ritonavir. Patients will be enrolled in community pharmacies that dispense the medicines prescribed in general practice. Both country-specific and pooled analyses of data from multiple countries are planned.

Globally, recruitment to CEM is expected to be slow because the number of COVID-19 infections has dropped since the peak of the pandemic. Another challenge is the time it takes to obtain protocol approvals and the differences in the approval process between countries. Often, specific training for ethics committees and other approval bodies to evaluate non-intervention study protocols, specifically for issues around personal data protection, is required.

On the other hand, the tailoring of the original protocol to support the monitoring of nirmatrelvir-ritonavir, without having to write a new protocol, demonstrates its flexibility.

Recommendations:

Based on the lessons learned, ACSoMP recommended that WHO considers the following to support CEM projects:

- Explore ways to sustain and utilize the infrastructure and capacity for CEM that were established during the COVID-19 pandemic, for example, the use of CEM to assess the safety of new and repurposed medicines in the future.
- Apply the lessons learned in managing funding, revision of study protocols, and lead time for approvals of future CEM projects in countries.
- Discuss these learnings during the next joint ACSoMP/GACVS meeting in November 2023, to optimize the implementation and use of CEM in pharmacovigilance.

Updated recommendations for valproic acid use in women and girls of childbearing potential

The updated Mental Health Gap (mhGAP) guidelines from WHO (being finalized), provide recommendations for all anti-seizure and bipolar disorder management medicines, not just valproic acid (and its sodium salt, sodium valproate), in women and girls of childbearing potential. It is strongly recommended that women with epilepsy should have their seizures controlled as well as possible, with the minimal dose of monotherapy antiseizure medicine and that valproic acid should not be given to women and girls of childbearing potential. A similar strong recommendation against valproic acid for women and girls of childbearing potential is included in the section on bipolar disorder management.

A safety statement was published on WHO's website⁴. The link to the statement was added to the mhGAP website⁵ and disseminated to relevant agencies, for example, to the UN Refugee Agency, United Nations Human Commissioner for Refugees (UNHCR). The next steps include a communication plan (e.g., press briefing) to ensure that the updated recommendations on valproic acid are disseminated to key stakeholders when the updated mhGAP guidelines are published in the second half of 2023. The key messages will be disseminated to non-governmental organizations (NGOs) and to national professional and patient organizations. The International Bureau for Epilepsy (IBE), an umbrella organization of national patient organizations is one NGO that is working closely with the Brain Health Unit of WHO for the dissemination of the mhGAP guidelines. The communication will include information about algorithms for alternative treatments and methods for medication switching. Local organizations will be involved in dissemination in low- and

⁴ WHO Statement on the risks associated with use of valproic acid (sodium valproate) in women and girls of childbearing potential. Geneva: World Health Organization (<https://www.who.int/news/item/02-05-2023-use-of-valproic-acid-in-women-and-girls-of-childbearing-potential>, accessed June 2023).

⁵ WHO mhGAP Intervention Guide - Version 2.0. Geneva: World Health Organization (<https://www.who.int/publications/i/item/9789241549790>, accessed June 2023).

middle-income countries (LMICs) to ensure more effective and user-friendly communication. The guidelines will be tailored to reflect the availability of alternative treatments in countries. In addition, the mhGAP derivative products (intervention guide, training manuals, e-learning course, and mhGAP app) will be updated.

In the recent 2023 meeting of the Expert Committee on WHO Model Lists of Essential Medicines, there was an application for the inclusion of levetiracetam on the Essential Medicines List (EML) and Essential Medicines List for Children (EMLc), supported by the Brain Health Unit. The outcomes from the meeting with the updated Model Lists will be published late June, but the application, expert reviews, and public and WHO comments, which were all favourable, are available online⁶. It was recognized by both the EML team and the Brain Health Unit that, having alternative treatments available on the EML list is critical to support the appropriate use of anti-seizure medicines by women of childbearing potential and by pregnant women.

Recommendations:

ACSoMP recommended a meeting between a few ACSoMP members and the Brain Health Unit in the coming weeks to discuss how to ensure effective communication of the updated recommendations.

Update on the use of valproic acid in men and the risk of neurodevelopmental disorders in the offspring

The post-authorization safety study (PASS) (risk management category 1) imposed on the MAH as a condition of the marketing authorization for valproic acid was discussed during a recent meeting of the European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC). This PASS is a population-based retrospective study to evaluate paternal exposure to valproic acid and the risk of neurodevelopmental disorders, including autism spectrum disorders and congenital abnormalities in offspring (EUPAS34201), using data from national registries in Norway, Denmark, and Sweden. The overall results show that there is a higher risk of developmental disorders in offspring aged 0 to 12 years following paternal exposure to valproic acid, although some differences were observed between the countries. No differences were observed for congenital abnormalities. Limitations of this PASS include country-specific differences in data collection and organization of healthcare systems. Also, according to PRAC, it is unclear what type of epilepsy was being treated with valproic acid and other anticonvulsants in the three countries. PRAC has sent additional questions to the MAH about these limitations and the underlying mechanisms for the epigenetic changes that could explain the results. ACSoMP will be informed about the PRAC recommendations as soon as these are available. Some actions have been taken outside of Europe as well. For example, the MAH, in collaboration with the Singapore authorities has sent a Direct Healthcare Professional Communication (DHPC) about the study findings and has already implemented additional risk minimization measures and updated the product information.

Recommendations:

WHO (Pharmacovigilance team and Brain Health Unit) is planning a survey on the impact of the updated recommendation for valproic acid use in women of childbearing potential. ACSoMP recommended adding questions to support the evaluation of the use of valproate in men who intend to become fathers.

Miltefosine and ocular events: update

A statement from ACSoMP on measures to minimize the risk of ocular adverse events associated with miltefosine was published on 12 April 2023⁷. The link to this statement was shared with various stakeholders. The first meeting of a WHO Guideline Development Group to develop the WHO clinical guidelines on leishmaniasis and to review the benefit-risk of miltefosine in its different indications, based on the conclusions from a multidisciplinary technical group (MTG), was held in April 2023.

A draft patient information brochure has been developed to facilitate communication on the risk of ocular adverse events with miltefosine. This brochure will need local adaptation and user testing and can then be printed and distributed by the national leishmaniasis programme. This brochure is not intended to replace the patient information leaflet, which is a regulatory document. The communication strategy will ensure that the

⁶ WHO A.24 Levetiracetam - epilepsy - EML and EMLc [website]. (<https://www.who.int/groups/expert-committee-on-selection-and-use-of-essential-medicines/24th-eml-expert-committee/a24-levetiracetam---epilepsy---eml-and-emlc>, accessed June 2023).

⁷ WHO Measures to minimize the risk of ocular adverse events with miltefosine [website]. (<https://www.who.int/news/item/12-04-2023-acsomp-miltefosine> accessed June 2023).

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information reaches all the relevant target audiences. The next steps include preparing a public assessment report, and, based on the lessons learned, developing a standard operating procedure (SOP) on how WHO can facilitate the assessment of serious adverse events reported with products used in public health programmes, and their timely communication.

Recommendations:

ACSoMP recommended that the project, on the assessment of ocular events with miltefosine, should be assessed to identify where task sharing, and other interventions could have ensured a timelier completion of the investigation. They advised that, based on the lessons learned, recommendations for improvements to make the process more efficient should be made.

Updates on malaria treatment during pregnancy

WHO has combined their guidelines for malaria treatment, vector control, etc. into one living document that is continually being updated as new evidence becomes available using WHO's transparent, rigorous guideline development process. The latest guidelines recommend that pregnant women with malaria should be treated in the first trimester with artemisinin-based combination therapies. The guidelines are available on the WHO website⁸, and can also be accessed through the MAGICapp⁹.

The risk of malaria is highest in the first and second trimesters of pregnancy. Up until November 2022, WHO recommended the use of quinine and clindamycin in the first trimester of pregnancy instead of artemisinin due to concerns about teratogenicity observed in pre-clinical animal studies.

The updated recommendations in 2022 were based on an updated systematic review of the evidence for the safety of artemisinin in the first trimester of pregnancy. A strong recommendation, with low certainty of evidence, was made to treat pregnant women with uncomplicated malaria in the first trimester with artemether-lumefantrine. There was insufficient evidence to make a definite recommendation for the use of artesunate-amodiaquine, artesunate-mefloquine, or dehydro-artemisinin piperazine. However, because of the lower efficacy and poorer tolerability of quinine treatment and the difficulties to ensure adherence to the seven-day multiple daily doses required for the standard course of quinine treatment, it was recommended that any of these could be used if artemether-lumefantrine is not available.

For these recommendations, pharmacovigilance, adverse events, and pregnancy outcome surveillance should be strengthened in countries, as when any new malarial treatment is implemented. The Program for Appropriate Technology in Health (PATH), in collaboration with WHO, has completed an extensive mapping exercise of existing pregnancy registries that were set up for different purposes in LMICs. The WHO Pharmacovigilance team will review the results from this mapping exercise, to identify registries that can be used when monitoring the safety of these antimalarials and other medicines and vaccines in pregnant women.

Recommendations:

The Committee recommended setting up a working group to identify what registries are available and can be used and to define a core data set to be captured, to monitor the safety of the antimalarials in pregnancy. The Committee recommended that the group also consider how ACSoMP can support the change in practice, for malaria treatment for pregnant women during their first trimester, including how pregnant women can be encouraged to share their data about their experience with malaria treatment during and after their pregnancy.

⁸ WHO Guidelines for malaria. Geneva: World Health Organization (<https://www.who.int/publications/i/item/guidelines-for-malaria>, accessed June 2023).

⁹ WHO Guidelines for malaria. Geneva: World Health Organization (<https://app.magicapp.org/#/guideline/7661>, accessed November 2023).

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