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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 recommendations from the fourth joint meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP) and the WHO Global Advisory Committee on Vaccine Safety (GACVS), 12-14 November 2024.

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All the previous issues of the WHO pharmaceuticals newsletter can be accessed from our website.

Darvadstrocel

Withdrawn from the EU market

Europe. The European Medicines Agency (EMA) announced that the Marketing Authorisation Holder (MAH) of darvadstrocel (Alofisel®) has decided to withdraw the medicine from the European Union (EU) market.

Darvadstrocel consists of mesenchymal stem cells derived from the fat tissue of adult donors and is classified as an advanced therapy medicinal product, specifically a 'stem cell therapy product'. It is used for the treatment of complex anal fistulas in adults with Crohn's disease (an inflammatory condition of the gut) when conventional or biological therapies have not been sufficiently effective.

Data from a recent study indicated that the benefit of darvadstrocel is no longer demonstrated and therefore does not outweigh the risks associated with its use.

As the MAH considered it was not possible to provide additional data on the effectiveness of the medicine as requested by the EMA, it has decided to withdraw darvadstrocel from the EU market.

Reference:
News, EMA, 13 December 2024 (link to the source within www.ema.europa.eu)

Glatiramer acetate

Risk of anaphylaxis

United States. The US Food and Drug Administration (FDA) has warned about the risk of anaphylaxis with the medicine glatiramer acetate (Copaxone®, Glatopa®), which is used to treat patients with multiple sclerosis (MS). FDA is adding a new Boxed Warning about this risk to the glatiramer acetate prescribing information and patient Medication Guide.

This serious allergic reaction can occur at any time while on treatment, after the first dose or after doses administered months or years after starting the medicine. For most patients who experienced anaphylaxis with glatiramer acetate use, the symptoms appeared within one hour of injection. In some cases, anaphylaxis resulted in hospitalization and death.

The initial symptoms of anaphylaxis can overlap with those of a common reaction called immediate post-injection reaction that is temporary and can start soon after a shot is given. While immediate post-injection reaction is common, anaphylaxis is rare and its symptoms are typically more severe, worsen over time, and require treatment. Patients experiencing a reaction after the medicine is administered should seek immediate medical attention if the symptoms are more than mild, get worse over time, or do not go away within a brief time.

FDA recommends that health-care professionals be aware that fatal anaphylaxis has occurred with glatiramer acetate, including cases reported years after treatment initiation and that the symptoms of these rare anaphylactic events may overlap with those of common immediate post-injection reactions.

Reference:
MedWatch, US FDA, 22 January 2025 (link to the source within www.fda.gov)

(See also WHO pharmaceuticals newsletter No.5, 2024: Glatiramer acetate and risk of anaphylactic reactions)

GLP-1 and dual GIP/GLP-1 receptor agonists

Risk of pulmonary aspiration during general anaesthesia or deep sedation

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has informed health-care professionals about the potential risk of pulmonary aspiration in patients using glucagon-like peptide-1 (GLP-1) or dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists who undergo surgery or procedures with general anaesthesia or deep sedation. New warnings have been added to the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets.

GLP-1 and dual GIP/GLP-1 receptor agonists are a class of medications that are used to treat type II diabetes mellitus and/or obesity. Residual gastric content is a

risk factor for aspiration in patients who undergo surgery or procedures with general anaesthesia or deep sedation. All GLP-1 and dual GIP/GLP-1 receptor agonists slow down gastric emptying, therefore patients taking these medicines may have a higher risk of pulmonary aspiration due to retained gastric contents. This can potentially lead to severe complications, such as aspiration pneumonia. Cases have been reported in the literature as well as through Yellow Card reports.

A recent European review of the available evidence for all GLP-1 and dual GIP/GLP-1 receptor agonists concluded that the data supports an association between GLP-1 or dual GIP/GLP-1 receptor agonists and the potential risk of pulmonary aspiration during anaesthesia or deep sedation because of the delayed gastric emptying associated with these medicines.

Reference:
Drug Safety Update, MHRA, 28 January 2025 (link to the source within www.gov.uk/mhra)

HMG-CoA reductase inhibitors

Risk of myasthenia gravis, including ocular myasthenia

Canada. Health Canada's review concluded that there is a possible link between HMG-CoA reductase inhibitors and the risk of myasthenia gravis, including ocular myasthenia, and that this is a class-effect**.** Health Canada will work with the manufacturers to update the product safety information in the Canadian product monograph (CPM) for HMG-CoA reductase inhibitors that are currently not labelled with the risk of myasthenia gravis, including ocular myasthenia.

HMG-CoA reductase inhibitors, more commonly known as statins, include products containing atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Myasthenia gravis, including ocular myasthenia, is a chronic autoimmune neuromuscular disorder characterized by weakness and rapid fatigue of voluntary muscles, including those that control the eyes and eyelids.

Health Canada reviewed 31 cases (2 Canadian and 29 international) of myasthenia gravis and/or ocular myasthenia in patients taking statins. Of the 31 cases, 27 (1 Canadian) were found to be possibly linked to the use of statins, 1 was unlikely to be linked and 3 (1 Canadian) could not be assessed due to missing information. Of the possible cases, 3 had recurrence of symptoms of myasthenia gravis and/or ocular myasthenia when treated with different statins, which suggests a drug class-effect for this risk.

Reference:
Monthly recap of health product safety information, Health Canada, January 2025 (link to the source within https://www.canada.ca).

(See also WHO pharmaceuticals newsletter No.2, 2023: Statins potential risks of myasthenia gravis and ocular myasthenia)

Isotretinoin

Risk of sacroiliitis

Canada. Health Canada's safety review found a possible link between isotretinoin and the risk of sacroiliitis, and will work with the manufacturers to update the product safety information in the Canadian product monograph (CPM) for isotretinoin-containing products to include the risk of sacroiliitis.

Isotretinoin is a prescription drug authorized for sale in Canada for the treatment of severe forms of acne in patients 12 years of age and older that should be used when the acne fails to respond to other treatments.

Health Canada reviewed 24 international cases of sacroiliitis in patients taking isotretinoin. Of those 24 cases, 23 were found to be possibly linked to the use of isotretinoin and 1 was unlikely to be linked. The average age was 20 years in cases where the age was provided. No deaths were reported among the 24 cases reviewed.
Health Canada also reviewed 18 articles published in the scientific literature. While the studies supported a link between the risk of sacroiliitis and the use of isotretinoin, they did not identify a clear biological mechanism to explain how isotretinoin use could lead to sacroiliitis.
In both the cases reviewed and the scientific literature, sacroiliitis improved after discontinuation of

isotretinoin and appropriate treatment.

Reference:

Monthly recap of health product safety information, Health Canada, March 2025 (link to the source within https://www.canada.ca)

Montelukast

Risk of neuropsychiatric effects

Australia. The Therapeutic Goods Administration (TGA) has added a new boxed warning about serious neuropsychiatric events with all montelukast products. These events include behavioural changes, depression and suicidal thoughts and behaviour.

Montelukast is a prescription medicine used to prevent and treat chronic asthma in adults and children aged 2 years and older, and for symptomatic seasonal allergic rhinitis (hay fever).

The following boxed warning is included in the Australian Product Information for montelukast products:

"WARNING: Serious neuropsychiatric events. Neuropsychiatric events such as behavioural changes, depression and suicidality have been reported in all age groups taking montelukast (see sections 4.4 and 4.8). Events are generally mild and may be coincidental. However, the symptoms may be serious and continue if the treatment is not withdrawn. Therefore, the treatment with montelukast should be discontinued immediately if neuropsychiatric symptoms occur during treatment. Advise patients and/or caregivers to be alert for neuropsychiatric events and instruct them to notify their physician if these changes in behaviour occur."

Reference:

Safety updates, TGA, 16 January 2025 (link to the source within www.tga.gov.au)

(See also WHO pharmaceuticals newsletter No.3, 2024: Montelukast and new boxed warning for the risk of neuropsychiatric events)

Oral anticoagulants

Risk of splenic rupture

Canada. Health Canada's safety review found a possible link between oral anticoagulants (apixaban-, dabigatran-, edoxaban-, rivaroxaban- and warfarin-containing products) and the risk of atraumatic (without apparent cause) splenic rupture. Health Canada will work with manufacturers to update the Canadian Product Monograph (CPM) for all oral anticoagulants to include this risk.

Health Canada reviewed 42 cases (3 Canadian and 39 international) of splenic rupture in patients taking oral anticoagulants, including 39 from the published literature. Of the 42 cases, 1 was found to be probably linked to the use of oral anticoagulants, 21 (1 Canadian) were found to be possibly linked, 16 were unlikely to be linked, and 4 (2 Canadian) could not be assessed due to missing information. Besides having taken oral anticoagulants, in 9 of the 21 possible cases, there was no other possible explanation (for example, trauma or existing medical condition) reported for the splenic rupture. However, atraumatic rupture of the spleen is known to occasionally occur.

Health Canada also reviewed the findings from a study that examined over 27,000 international reports of suspected adverse drug reactions associated with oral anticoagulants. The findings showed that events of splenic rupture were more frequently reported than expected with these drugs, thereby supporting a link.

Reference:

Monthly recap of health product safety information, Health Canada, March 2025 (link to the source within https://www.canada.ca)

RSV vaccines

Risk of Guillain-Barré syndrome (GBS)

United States. The US FDA has required and approved safety labeling changes to the Prescribing Information for Respiratory Syncytial Virus (RSV) vaccine (Abrysvo® and Arexvy®). Specifically, FDA has required each vaccine to include a new warning about the risk for Guillain-Barré syndrome (GBS) following administration of their RSV vaccine. The Prescribing Information for each vaccine has been revised to include the following language in the Warnings and Precautions section:

- Abrysvo®- The results of a postmarketing

observational study suggest an increased risk of GBS during the 42 days following vaccination with Abrysvo®.

- Arexvy®- The results of a postmarketing observational study suggest an increased risk of GBS during the 42 days following vaccination with Arexvy®.

GBS is a rare disorder in which the body's immune system damages nerve cells, causing muscle weakness and sometimes paralysis.

Reference:

MedWatch, US FDA, 7 January 2025 (link to the source within www.fda.gov)

Tegafur / gimeracil / oteracil

Risk of hyperammonaemia

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has requested that the Marketing Authorisation Holder (MAH) of Tegafur / gimeracil / oteracil (Teysuno®) update the summary of product characteristics (SmPC) and the package leaflet to include the risk of hyperammonaemia.

Teysuno® is a cancer medicine containing the active substances tegafur, gimeracil and oteracil. It belongs to a group of cancer medicines called fluoropyrimidines and is used to treat advanced gastric (stomach) cancer and metastatic colorectal cancer (cancer of the colon and rectum that has spread elsewhere in the body).

PRAC has considered the available evidence in EudraVigilance and the literature, the cumulative review submitted by the MAH and also biologically plausible mechanism, and has agreed that a causal association between Teysuno® and hyperammonaemia is at least a reasonable possibility.

PRAC has recommended that the SmPC be updated to include the following information: Hyperammonaemia has been observed with Teysuno®. In patients who develop unexplained neurologic symptoms (like ataxia, lethargy or changes in mental status), ammonia levels should be measured and appropriate clinical management should be initiated. If hyperammonaemia neurologic symptoms worsen to hyperammonaemic encephalopathy, discontinuation of Teysuno® should be considered.

Reference:
PRAC recommendations on signals, EMA, 7 April 2025 (link to the source within www.ema.europa.eu)

Topiramate

Risk of neurodevelopmental disorders

South African. The South African Health Products Regulatory Authority (SAHPRA) has reminded health-care professionals about the risk of neurodevelopmental disorders in the children born to women exposed to topiramate during pregnancy. The Professional Information (PI) and Patient Information Leaflet (PIL) will be updated accordingly.

Topiramate is indicated to treat epilepsy. Topiramate can cause major congenital malformations and foetal growth restriction when used during pregnancy. Recent data also suggests that topiramate use during pregnancy may increase the risk of neurodevelopmental disorders (NDD) including autism spectrum disorders, intellectual disability and attention deficit hyperactivity disorder (ADHD).

Health-care professionals should ensure that women of childbearing potential treated with topiramate are fully informed of the known and potential risks related to the use of topiramate during pregnancy and the need for highly effective contraception.

Reference:
Communication to health care professionals, SAHPRA, 12 March 2025 (link to the source within www.sahpra.org.za)

(See also WHO pharmaceuticals newsletter No.2, 2024: Topiramate and risk of neurodevelopmental disorders in children exposed in-utero)

Fezolinetant

Risk of drug-induced liver injury

Europe. EMA has reminded health-care professionals that serious liver injury has been observed with fezolinetant (Veoza®), and liver function tests (LFTs) must be performed prior to initiation of fezolinetant.

Fezolinetant is indicated for the treatment of moderate to severe vasomotor symptoms (VMS) - hot flushes and night sweats - associated with menopause.

Treatment with fezolinetant must not be initiated if serum alanine aminotransferase (ALT) or serum aspartate aminotransferase (AST) levels are ≥2x ULN or if total bilirubin levels are ≥2x ULN. During the first three months of treatment, monthly LFTs must be performed, and thereafter based on clinical judgement. LFTs must also be performed when symptoms suggestive of liver injury occur.

Patients must be advised to immediately seek medical attention if they experience signs or symptoms that may suggest liver injury such as fatigue, pruritus, jaundice, dark urine, pale faeces, nausea, vomiting, decreased appetite and/or abdominal pain.

Reference:
Direct healthcare professional communication, EMA, 23 January 2025 (link to the source within www.ema.europa.eu)

Naltrexone / bupropion

New risk minimisation measures

Europe. The human medicines committee (CHMP) of the EMA has finalised its review of naltrexone / bupropion (Mysimba®) and concluded that the benefits of Mysimba® continue to outweigh its risks. However, the MAH must provide more information from an ongoing study on the medicine's cardiovascular effects in patients treated for longer than one year. New measures are also being implemented to minimise potential cardiovascular risks with long-term use.

At the time of Mysimba®'s authorization, CHMP noted uncertainties regarding the long-term effects of Mysimba® on the cardiovascular system. To date, studies have shown that there is no cardiovascular safety concern when Mysimba® is used for up to 12 months. However, the data available are not sufficient to fully determine the cardiovascular safety beyond this time.

CHMP has agreed that an ongoing safety study with Mysimba® in patients with obesity or overweight carried out by the MAH is appropriate to generate evidence about this risk in the long term. The results are expected in 2028, and the MAH must provide annual reports on the progress of the study. The CHMP has imposed this study as a condition to the marketing authorization.

In addition, further measures will be implemented to minimize potential cardiovascular risks with long-term use. Treatment with Mysimba® should be stopped after one year if weight loss of at least 5% of the initial body weight is not maintained. In addition, health-care professionals should carry out a yearly assessment and discuss with their patients whether Mysimba® remains beneficial for them, taking into account any changes to their cardiovascular risk and whether weight loss has been maintained.

Reference:
News, EMA, 28 March 2025 (link to the source within www.ema.europa.eu)

Rifampin

Risk of increased blood uric acid levels

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has reminded health-care professionals about the risk of increased blood uric acid levels associated with the use of rifampin.

Rifampin belongs to the antimicrobial class of drugs and is used to manage and treat various mycobacterial infections and gram-positive bacterial infections.

The SFDA searched the

Saudi national database and the WHO VigiBase, identifying 844 international cases and one local case. Using the WHO-UMC causality assessment criteria on the extracted ICSRs with a completeness score of 1.0, the SFDA identified 30 cases: 28 cases were assessed as possibly linked to rifampin, while the remaining two were assessed as unlikely.

Disproportionality analysis using the WHO-UMC information component (IC) yielded a value of 5.5, indicating a strong statistical association. Additional evidence from the literature also supports this signal.

These findings highlight the need for health-care professionals to monitor blood uric acid levels in patients receiving rifampin therapy.

Reference:
Safety Alerts, SFDA, February 2025 (link to the source within www.sfda.gov.sa)

Risperidone

Risk of medication errors

Ireland. The Health Products Regulatory Authority (HPRA) has reminded health-care professionals about the risk of medication errors leading to accidental overdoses involving risperidone oral solution in children and adolescents. The majority (74%) of reported overdose cases were serious. The most frequent incidents were linked to decimal point errors, resulting in 10-fold overdosing.

These errors were primarily attributed to small dose volumes prescribed for the paediatric population (0.25–1.5 ml) which may cause confusion when adminstered with dosing devices which can contain much larger volumes.

Health-care professionals are advised to provide clear guidance to caregivers and patients on the correct use of dosing devices and emphasise the importance of reading the package leaflet to ensure safe and accurate dosing.

Reference:
Safety notices, HPRA, 28 February 2025 (link to the source within www.hpra.ie)

Semaglutide

Risk of non-arteritic anterior ischemic optic neuropathy (NAION)

Europe. The PRAC of the EMA has started a review of medicines containing semaglutide following concerns regarding an increased risk of developing NAION, a rare eye condition, as suggested in two recent observational studies.

Semaglutide, a GLP-1 receptor agonist, is the active substance in certain medicines used in the treatment of diabetes and obesity (namely Ozempic®, Rybelsus® and Wegovy®).

PRAC is assessing whether patients treated with semaglutide may have an elevated risk of developing NAION. This is a disorder caused by reduced blood flow to the optic nerve in the eye with potential damage to the nerve, which can lead to loss of vision in the affected eye. Patients with type 2 diabetes might already have an inherently higher risk of developing this condition.

PRAC will now review all available data on NAION with semaglutide including data from clinical trials, post-marketing surveillance, studies on the mechanism of action and the medical literature (including the results of the observational studies).

Reference:
News, EMA, 17 January 2025 (link to the source within www.ema.europa.eu)

Systemic fluoropyrimidines

Risk of severe toxicity in patients with dihydropyrimidine dehydrogenase deficiency

Canada. Health Canada recommends that testing for dihydropyrimidine dehydrogenase (DPD) deficiency be considered before treatment with systemic fluoropyrimidines.

Systemic fluoropyrimidines are a class of prescription drugs that includes capecitabine tablets and fluorouracil (5-fluorouracil) injection, and are authorized to treat various types of cancers alone or in combination with other drugs.

Between January 1, 2019 and February 5, 2025, Health Canada received 10 Canadian reports of adverse reactions involving severe toxicity associated with systemic fluoropyrimidines (6 related to capecitabine tablets and 4 to fluorouracil injection) in patients with DPD deficiency. Of the 10 cases, 6 had a fatal outcome. Of the 6 fatal cases, one involved prospective DPYD genotype testing that failed to identify the patient's DPD deficiency. Variations in the DPYD gene were later confirmed upon full gene sequencing. For the other 5 fatal cases, it could not be confirmed whether DPYD genotype testing failed to identify the patient's DPD deficiency due to limited available information.
Health Canada recommends that health-care professionals be aware of the risks associated with DPD deficiency and inform patients prior to treatment about the potential for serious or life-threatening adverse reactions. Testing for DPD deficiency should be considered before treatment with capecitabine tablets and fluorouracil injection, based on local availability and current guidelines.

Reference:
Monthly recap of health product safety information, Health Canada, March 2025 (link to the source within https://www.canada.ca)

Thiocolchicoside containing medicines

Risk of genotoxicity

Egypt. The Egyptian Pharmacovigilance Center (EPVC) of the Egyptian Drug Authority (EDA) has reminded health-care professionals about the risk of genotoxicity associated with thiocolchicoside containing medicines.

Thiocolchicoside is a muscle relaxant widely used for managing painful muscle spasms.

Contraindications for use of thiocolchicoside containing medicines for systemic use has been extended to include:

- Men who are not willing to use effective contraceptive measures during treatment and for 3 months after stopping treatment, to avoid conception and any consequent risks to the fetus;
- Women of childbearing age who do not use effective contraceptive methods even for 1 month after stopping treatment, to avoid pregnancy and any consequent risks for the fetus.

Health-care professionals are reminded that the use of systemic thiocolchicoside is limited to the short-term adjuvant treatment of painful muscle contractures in acute spinal disorders in adults and adolescents aged 16 years and older. The maximum recommended daily doses and duration of treatment are, respectively, 16 mg per day for up to 7 days orally, 8 mg per day for up to 5 days intramuscularly.

Reference:
Newsletter, EDA, March 2025 (link to the source within www.edaegypt.gov.eg)

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

Recommendations from the fourth joint meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP) and the WHO Global Advisory Committee on Vaccine Safety (GACVS)

12-14 November 2024

WHO convened the fourth joint meeting of the **WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)** and the **WHO Global Advisory Committee on Vaccine Safety (GACVS) from 12 to 14 November 2024.**

The Global Advisory Committee on Vaccine Safety (GACVS) was established in 1999, and the Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003, to provide independent, authoritative, scientific advice to the World Health Organization (WHO), respectively, on vaccine and medicine safety issues of global or regional concern.

The 3-day meeting of ACSoMP and GACVS, 12–14 November 2024 included topics specific to vaccine safety, pharmacovigilance issues common to both vaccines and medicines, and topics specific to medicine safety. A summary of the presentations and recommendations from the medicine specific sessions is provided below. A summary of the discussions and recommendations related to vaccine safety and sessions of common interest for pharmacovigilance of both medicines and vaccines are published in the WHO *WER*.[1]

Safety of arpraziquantel (arPZQ) for schistosomiasis in children

Ongoing initiatives are preparing for the introduction of pediatric praziquantel formulation to treat schistosomiasis in young children. In December 2023, the EMA adopted a positive opinion for arPZQ, and in May 2024, the WHO included arPZQ 150 mg dispersible tablets in its list of Prequalified Medicines. The UNDP-led Access and Delivery Partnership (ADP) has been working with Ghana, Senegal, and Tanzania on the rollout of arPZQ. ADP plans to support national neglected tropical disease (NTD) programs and pilot the rollout in selected districts in 2025.

ADP has been strengthening health systems in these countries over the past 18 months. In 2025, ADP will continue supporting pilot programs and addressing challenges such as financing, health system functioning, and knowledge sharing. The WHO's Pharmacovigilance Team has also developed a workplan for arPZQ in these countries, focusing on safety monitoring and pharmacovigilance practices.

Tanzania has not yet begun the arPZQ rollout but has conducted surveys to determine the burden of schistosomiasis and is exploring the best delivery methods. The country has requested support from WHO for pharmacovigilance activities, including training and surveillance protocols.

Merck's safety data from clinical studies in children aged 3 months to 6 years show that arPZQ has a favourable safety profile, similar to that of PZQ. However, challenges remain in monitoring safety for children under one year of age. The Committees discussed the need for active surveillance and how existing

[1] Report of the 4th joint meeting of the WHO Global Advisory Committee on Vaccine Safety and the Advisory Committee on Safety of Medicinal Products, 12–14 November 2024. https://iris.who.int/handle/10665/380715

data on PZQ might inform the safe use of arPZQ, especially in light of limited safety data in children under one year of age.

Recommendations:
The Committee made recommendations on the future safety monitoring of arPZQ in pediatric populations as follows:

- When developing further pharmacovigilance country workplans and related documents, all relevant pharmacovigilance stakeholders working on the initiatives (e.g., Public Health Practitioners (PHPs), National Regulatory Authorities (NRAs), WHO, marketing authorization holders (MAHs)/manufactures, etc.) must be engaged to ensure pharmacovigilance activities are collaboratively conducted under concurrence by NRAs, and that planned pharmacovigilance activities are anchored into the national institutional development plans.
- Avoid parallel data collection systems in country, and instead aim to rely on the existing systems as much as possible.
- Explore potential additional pharmacovigilance activities such as CEM.
- NRAs are strongly encouraged to collect arPZQ/PZQ safety reports associated with pediatric population from relevant national stakeholders (PHPs, HCPs, patients, MAHs) and to submit to VigiBase in a timely manner.
- WHO is encouraged to coordinate a platform that includes relevant stakeholders and experts, with the aim of developing tools to support LMICs to perform pharmacovigilance in pediatric populations (e.g., a practical guidebook). This work might involve learnings from experiences of arPZQ-related initiatives.
- Explore if arPZQ could be a good candidate for applying the Smart Surveillance Strategy.

Safety of the RSV monoclonal antibody, nirsevimab

Nirsevimab (AstraZeneca, Sanofi) is a long-acting monoclonal antibody targeting the prefusion respiratory syncytial virus (RSV) F protein. Approved in over 40 countries, it has demonstrated high effectiveness and a favourable safety profile in clinical trials and post-market studies.

Clinical trial data on nirsevimab, involving 2,966 infants receiving the 50 mg dose and 1,259 placebo participants, showed no serious adverse events related to the product. There were six deaths in the intervention group and three in the placebo group, but none were linked to nirsevimab. Nine adverse events of special interest (AESIs) occurred in the intervention group, compared to three in the placebo group. No safety concerns were found regarding coadministration with other childhood vaccines, and the safety profile was similar to when vaccines are administered alone.

In the United States, nirsevimab is approved for preventing RSV lower respiratory tract disease in newborns, infants during their first RSV season, and vulnerable children up to 24 months during their second season. As of June 30, 2024, the most frequent adverse events reported to the FDA Adverse Event Reporting System (FAERS) included drug ineffectiveness (30.3%), RSV bronchiolitis (27.3%), and bronchiolitis (13.8%). Most reported adverse events involved breakthrough RSV infections after nirsevimab administration, with additional reports of medication errors and hypersensitivity reactions.

The Committee discussed the use of nirsevimab in various contexts, including its coadministration with childhood vaccines, its effectiveness in preventing RSV infections, hypersensitivity reactions after repeated

doses, and its use following maternal RSV vaccination. These areas are important for ongoing monitoring and assessment.

Recommendations:
The Committee made recommendations for safety monitoring of nirsevimab as follows:

Continue to monitor further, particularly investigating:

- frequent and rare adverse events, including long term events in children
- events following coadministration of nirsevimab (in babies) and vaccines in mothers – especially if in future vaccines for children are developed
- adverse events following products in sequence (monoclonal antibody and other vaccines)
- dose administration for older children in terms of hypersensitivity reactions in older children

Safety of malaria medicines

The risk of malaria is highest in the first and second trimesters of pregnancy. Until November 2022, WHO recommended quinine and clindamycin for treating P. falciparum malaria in the first trimester due to concerns about artemisinin's safety. However, based on new evidence, WHO now recommends artemether-lumefantrine (AL) as the preferred treatment for uncomplicated malaria in the first trimester.

The Safety of Antimalarials in the FIrst TRimEster (SAFIRE) Consortium is conducting a phase IIIb trial to assess the safety, tolerability, and efficacy of antimalarials for treating P. falciparum malaria in the first trimester. This multicenter, non-inferiority trial will compare treatments, including pyronaridine–artesunate (PA) and dihydroartemisinin–piperaquine (DP), with AL in Mali, Burkina Faso, and Kenya. The primary outcome is the efficacy of the drugs, while the key safety outcome focuses on miscarriage, stillbirth, or fetal loss.

The WHO is updating guidelines on glucose-6-phosphate dehydrogenase (G6PD) testing for the safe use of tafenoquine and primaquine, which can cause severe hemolytic anemia in G6PD-deficient individuals. WHO's updated guidelines, published on 30 November 2024[2], include recommendations on G6PD testing to prevent adverse events.

Discussions/conclusions:
The Committee discussed the availability of safety data on primaquine, the low reporting of adverse events, and the anticipated costs of implementing G6PD testing. No recommendations were issued, and the Committee looks forward to the SAFIRE trial results.

Safety of therapeutics for HIV, hepatitis, and sexually transmitted infections (STIs) in pregnancy

In 2022, WHO recommended long-acting injectable cabotegravir (CAB-LA) as an additional HIV prevention option for those at high risk. While efficacy data for CAB-LA is robust, more safety data during pregnancy are needed. Ongoing studies aim to provide critical information, including safety during pregnancy and

[2] World Health Organization 2024. *WHO guidelines for malaria*. https://www.who.int/publications/i/item/guidelines-for-malaria (Accessed on 24 March 24, 2025)

breastfeeding. The Committee was updated on safety data for CAB-LA, lenacapavir (LEN), and the dapirivine (DPV) ring for HIV prevention and treatment during pregnancy.

Safety data from several trials indicate that CAB-LA and LEN have similar pregnancy outcomes to no exposure or oral pre-exposure prophylaxis (PrEP). For CAB-LA, data from 288 pregnancies show that dosing during pregnancy is appropriate, with no adverse effects. Similarly, LEN exposure in 105 pregnancies showed no significant differences in outcomes compared to oral PrEP. DPV ring data from 553 pregnancies also show no adverse effects.

Research on new antiretrovirals (ARVs) in pregnancy is progressing slowly, with 11 planned CAB-LA implementation studies, although most are not enrolling pregnant women. The first pregnancy outcome data are expected by late 2024, but analysis may not be available until 2025 or later.
The HIV Hepatitis STI Pregnancy Therapeutics Working Group has been updating WHO guidelines on PrEP and launching a new toolkit for ARV research in pregnancy. They are also working on harmonizing data from trials and surveillance programs, with plans to prioritize syphilis-related research in 2025.

The Committee discussed the importance of linking records across a woman's life to track the impacts of ARV exposure.

Recommendations:
The Committee made recommendations for supporting the safe use of HIV, hepatitis, and STI therapies in pregnancy as follows:

- Continue the work of the Pregnancy Therapeutic Working Group, in particular to follow up on the safety surveillance of LA-ARVs for HIV prevention and treatment (CAB-LA, LEN): to ensure collection of long-term safety data on their use in pregnancy; to enable capturing of unknown or rare events; to follow up on pharmacokinetics data to monitor events through breastfeeding; and to continue efforts to ensure harmonization to achieve comparability between studies, update the toolkit for research in pregnancy, and extend the work to syphilis.
- Follow up with relevant stakeholders to facilitate and accelerate research inclusive of pregnant and breastfeeding women for new long-acting HIV agents and inform WHO ARV optimization work on safety in pregnancy for both prevention and treatment.
- Continue monitoring and reporting to WHO ASCoMP on the latest results of the safety studies to support guideline revisions and recommendations by WHO.

Update on valproate usage in women and girls of childbearing potential

Despite being a known teratogen, valproate (sodium valproate, valproic acid, divalproex) continues to be used in pregnant women, particularly in low- and middle-income countries (LMICs). Factors such as lack of access to safer alternatives and the therapeutic advantages of valproate contribute to its continued use. WHO has updated guidelines to strengthen recommendations against using valproate in women and girls of childbearing potential with epilepsy.

In the South-East Asia Region (SEARO), a working group within the South-East Asia Regulatory Network (SEARN) is addressing sodium valproate use, aiming to improve knowledge on its benefit/risk balance and develop strategies to minimize risks. The first session is scheduled for early 2025.

WHO is also supporting countries to conduct a study on sodium valproate usage in LMICs among women and girls of childbearing age. This includes a cross-sectional hospital-based study and a mixed-methods study in healthcare and community settings. The Committee provided feedback on the study's design and conduct.

WHO and partners have been working to disseminate the updated mhGAP guidelines on valproate use in women of childbearing potential. A webinar on pregnancy and epilepsy and an eLearning course on valproate use were recently launched.

The Committee discussed WHO's efforts to monitor global valproate usage and minimize teratogenic risk. They also provided feedback on the WHO study, including suggestions to incorporate qualitative work and expand the scope to other epilepsy treatments, as well as addressing potential ethical concerns.

Recommendations:
The Committee made recommendations as follows:

Recommendations for supporting risk minimization efforts

- Efforts to support regulatory harmonization of risk minimization efforts relating to valproate use in women of childbearing potential (WOCBP) in the SEARO region are supported with recommendations from ACSoMP to expand such efforts to other regions.

Recommendations for the WHO study on sodium valproate usage

- The Committee supports the creation of a protocol to assist countries in assessing:
    - The extent to which and WOCBP are being treated with valproate products. Consideration should be given to expanding the study to include other anti-seizure medicines (e.g. carbamazepine, phenobarbital and topiramate).
    - The reasons for continued use of valproate products in pregnancy. The contribution of factors such as costs and availability of alternatives need to be explored. Understanding which women are prescribed valproate products and why would be important to understand.
    - The extent to which prescribers and women using valproate products are knowledgeable of the risks.
- There was general support for both quantitative and especially qualitative elements to the protocol.
- ACSoMP will continue to monitor this issue and looks forward to receiving any updates on the mhGap guidelines, drug utilization studies and regulatory risk minimization measures being undertaken in SEARO as well as other regions.

Safety of tecovirimat for treatment of mpox

In July 2022, WHO declared a Public Health Emergency of International Concern (PHEIC) due to a multi-country mpox outbreak. A PHEIC was again declared in August 2024 due to the resurgence of mpox in Africa, particularly affecting high-risk groups such as pregnant women and children. Tecovirimat, used for treating smallpox, mpox, and cowpox, is indicated for adults and children weighing at least 13kg.

The European Medicines Agency (EMA) reported that tecovirimat has mild adverse reactions including headache, dizziness, and nausea, with no significant risks identified. However, data on its use in pregnancy, breastfeeding, and immunocompromised patients is lacking. The most recent safety update (July 2023–January 2024) recommended that tecovirimat be taken with a fat-containing meal to improve absorption. Future updates may address its use in immunocompromised patients, neurotoxicity, anemia, and effectiveness against mpox Clade Ib infections.

Discussions and conclusions:

The Committee discussed the need for more evidence on appropriate pediatric dosing, resistance risks, metabolism, interactions, costs, and safety data from countries using tecovirimat. It was highlighted that there is a possible lack of efficacy due to inadequate gastrointestinal absorption when the medicine is taken with food which does not contain enough fat, and clearer text for patients has been proposed.

Safety of fexinidazole for treatment of Human African Trypanosomiasis (HAT)

HAT, or sleeping sickness, is lethal without treatment. Fexinidazole obtained a positive scientific opinion through Article 58 (now known as EUM4ALL) by the EMA for treatment of T. gambiense HAT in November 2018. In December 2023 this was extended to T. rhodesiense HAT. The WHO Therapeutic Guidelines were updated in June 2024.[3]

Fexinidazole is the first oral treatment for Human African Trypanosomiasis (HAT), but despite being oral, its use remains challenging. It requires a 10-day course with dose adjustments and must be taken with food. Common side effects include vomiting, nausea, and psychiatric issues such as insomnia, psychosis, depression, and anxiety. Due to safety concerns, WHO is closely monitoring its use. A phase 3 post-authorization safety study is being conducted in partnership with Sanofi, which lacks a field presence in HAT treatment. The study, led by WHO, aims to strengthen local pharmacovigilance and has shown that safety findings align with clinical trials, with good efficacy data.

In Europe, physicians face challenges accessing fexinidazole for rhodesiense HAT cases, as the drug is not approved for use in Europe.

The Committee acknowledged the update made on the new WHO guidelines for treatment of rhodesiense HAT and discussed difficulties in collecting data on psychiatric side effects in the ongoing study, suggesting the need for culturally tailored data collection methods.

Recommendations:

- The Committee acknowledged the progress made on the WHO/Sanofi post-authorization CEM study so far and recommended that new data from the study be made available to the Committee in the future (final report expected in 2026).

The Committee recommends all relevant pharmacovigilance stakeholders working on health programs (e.g., PHPs, NRAs, WHO etc.) engage in the future. The Committee emphasised the importance of tailoring PV and risk minimisation measures for the region/s where it will be used. These measures should ensure education, training and surveillance on the psychiatric adverse effects such as depression and suicidal ideation which can lead to suicide.

[3] World Health Organization 2024. Guidelines for the treatment of human African trypanosomiasis (https://www.who.int/publications/i/item/9789240096035). (Accessed on 21 March 2025)