WHO Vision for Safety of Medicinal Products

No country left behind:
worldwide pharmacovigilance for safer medicinal products,
safer patients

The aim of the newsletter is to disseminate regulatory information on the safety of medicinal products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Pharmacovigilance, MHP/RPQ, World Health Organization, 1211 Geneva 27, Switzerland,

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

In addition, this edition includes summary and recommendations from the third joint meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and WHO Global Advisory Committee on Vaccine Safety (GACVS) held 13-15 November 2023.

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### Feature

Summary and recommendations from the third joint meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) and WHO Global Advisory Committee on Vaccine Safety (GACVS), 13-15 November 2023

All the previous issues of the WHO Pharmaceuticals Newsletter can be accessed from our website.
Acetazolamide

Risks of choroidal effusion and choroidal detachment

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has recommended updating the product information for acetazolamide to include the risks of choroidal effusion and choroidal detachment (decrease in vision or pain in the eyes due to accumulation of fluid in the vascular layer of the eye behind the retina).

Acetazolamide is an inhibitor of carbonic anhydrase and is indicated for the treatment of glaucoma.

Cases of choroidal effusion/detachment have been reported after the use of acetazolamide. Symptoms include acute onset of decreased visual acuity or ocular pain and can occur within hours after initiation of acetazolamide treatment. If choroidal effusion/detachment is suspected, acetazolamide should be discontinued as rapidly as possible.

Reference:
PRAC recommendations on signals, EMA, 25 September 2023 (link to the source within www.ema.europa.eu)

(See also WHO Pharmaceuticals Newsletter No. 2, 2021: Diuretics, including acetazolamide and Risk of eye disorders in Canada)

Azacitidine

Risk of cutaneous vasculitis

Europe. The PRAC of the EMA has recommended updating the product information for azacitidine injectable formulations to include the risk of cutaneous vasculitis (inflammation of blood vessels in the skin which may result in rash).

Azacitidine is a type of cancer chemotherapy drug and is indicated for the treatment of myelodysplastic syndromes and chronic myelomonocytic leukaemia. Oral dosage form and injectable formulations are available, of those injectable formulations are subject to this safety update.

Having considered evidence in EudraVigilance and literature, the PRAC has agreed that a causal relationship between azacitidine injectable formulations and cutaneous vasculitis is at least a reasonable possibility.

Reference:
PRAC recommendations on signals, EMA, 23 October 2023 (link to the source within www.ema.europa.eu)

Isotretinoin

Potential risks of mental health and sexual function adverse reactions

1. United Kingdom. The MHRA has announced that the product information for isotretinoin has been updated to include new warnings and precautions on potential mental health and sexual function adverse reactions and requirement for two healthcare professionals to agree that there is no other appropriate effective treatment in patients under 18 years of age.

Isotretinoin (only capsule form is available in UK, Roaccutane® and Reticon®) is indicated for severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

The Isotretinoin Implementation Advisory Expert Working Group, formed by the Commission on Human Medicines (CHM), developed guidance on the assessment and monitoring of mental health and sexual function. Also, new compulsory regulatory risk minimisation materials have been developed for use with all patients. See link in the reference for further information on the risk minimization measures.

Reference:
Drug Safety Update, MHRA, 31 October 2023 (link to the source within www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No. 3, 2023: Isotretinoin and Risk of sexual dysfunction in UK)

2. Singapore. The Health Sciences Authority (HSA) has re-evaluated whether
the existing safety measures on isotretinoin oral forms should be further strengthened. Based on the current available information including the newly introduced measures by the MHRA as above, HSA, in consultation with its Product Vigilance Advisory Committee (PVAC), has concluded that the benefit-risk profile of isotretinoin remains favourable for its approved indications and the current product labelling is sufficient to mitigate both safety concerns.

The local product information of isotretinoin currently already contains warnings on psychiatric disorders and sexual dysfunction. Patient educational materials for isotretinoin are available on publicly accessible platforms, including the Medication Information Leaflets (MILs) on HealthHub.

Reference:
Announcements, HSA, 15 December 2023 (link to the source within www.hsa.gov.sg)

Levetiracetam, clobazam

Risk of drug reaction with eosinophilia and systemic symptoms (DRESS)

United States. The US Food and Drug Administration (FDA) is warning that levetiracetam and clobazam can cause drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS is a rare but serious reaction that can be life-threatening if not diagnosed and treated quickly. It may start as a rash but can quickly progress, resulting in injury to internal organs, the need for hospitalization, and even death.

Levetiracetam is an antiseizure medicine approved for use alone or with other medicines to control certain types of seizures in adults and children such as partial seizures, myoclonic seizures, or tonic-clonic seizures. Clobazam is a benzodiazepine indicated for use in combination with other medicines to control seizures in adults and children 2 years and older who have a specific severe form of epilepsy called Lennox-Gastaut syndrome.

Health-care professionals should be aware that prompt recognition and early treatment is important for improving DRESS outcomes and decreasing mortality. DRESS can develop 2-8 weeks after starting the medicines, and symptoms and intensity can vary widely.

Reference:
MedWatch, US FDA, 28 November 2023 (link to the source within www.fda.gov)

Omega-3-acid ethyl esters

Risk of atrial fibrillation

Europe. The PRAC of the EMA agreed to add atrial fibrillation (irregular, rapid contraction of the heart) as an adverse event to the product information for medicines containing omega-3-acid ethyl esters. Medicines containing omega-3-acid ethyl esters are indicated for the treatment of hypertriglyceridaemia, when a modification of diet and lifestyle alone are not sufficient to bring down levels of triglyceride in the blood.

The PRAC considered the results of systematic reviews and meta-analyses of randomised controlled clinical trials which highlighted a dose-dependent increased risk of atrial fibrillation in patients with established cardiovascular diseases or cardiovascular risk factors treated with omega-3-acid ethyl esters compared to placebo.

If atrial fibrillation develops, treatment by Omega-3-acid ethyl esters should be permanently discontinued. A Direct Healthcare Professional Communication (DHPC) will be sent shortly to provide health-care professionals with further details of this risk.

Reference:
Patients and carers, EMA, 29 September 2023 (link to the source within www.ema.europa.eu)

Pegcetacoplan

Risks of retinal vasculitis and retinal vascular occlusion

United States. The US FDA has updated the
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product information for pegcetacoplan (Syfovre®) to include the risks of retinal vasculitis and retinal vascular occlusion.

Pegcetacoplan is a complement inhibitor indicated for the treatment of geographic atrophy secondary to age-related macular degeneration (AMD).

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with use of pegcetacoplan. Cases may occur with the first dose of pegcetacoplan and may result in severe vision loss. Health-care professionals should discontinue treatment with pegcetacoplan in patients who develop these events and instruct patients to report any change in vision without delay.

Reference:
New Safety Information, US FDA, November 2023 (link to the source within www.fda.gov)

Pegfilgrastim, filgrastim, lenograstim

Potential risks of myelodysplastic syndrome and acute myeloid leukemia

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for pegfilgrastim, filgrastim, and lenograstim will be updated to include the potential risks of myelodysplastic syndrome and acute myeloid leukemia. Pegfilgrastim, filgrastim, and lenograstim are recombinant granulocyte colony-stimulating factors, a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream, and are indicated for the prevention of chemotherapy-induced febrile neutropenia. An observational study performed in the US has reported an increased risk of myelodysplastic syndrome or acute myeloid leukemia in patients with breast or lung cancer who were treated with pegfilgrastim or filgrastim in conjunction with chemotherapy. Although the causal relationship of these medicines to myelodysplastic syndrome or acute myeloid leukemia is not clear, patients should be carefully monitored after administration of the medicines.

Reference:
Revisions of precautions, MHLW/PMDA, 12 October 2023 (link1 and link2 to the source within www.pmda.go.jp/english)

Pseudoephedrine

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

Europe. The PRAC of the EMA has recommended new measures for medicines containing pseudoephedrine to minimise the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS). PRES and RCVS are rare conditions that can involve reduced blood supply to the brain, potentially causing serious, life-threatening complications. With prompt diagnosis and treatment, symptoms of PRES and RCVS usually resolve. The recommendation has been also endorsed by the Committee for Medicinal Products or Human Use (CHMP) of the EMA. Pseudoephedrine is a stimulant that is often used as a decongestant in people who have a cold or allergies. Several pseudoephedrine containing products are available as over-the-counter (OTC) medicines. The PRAC reviewed evidence including post-marketing safety data, which showed that pseudoephedrine is associated with risks of PRES and RCVS. The product information will be updated to include the risks and the new measures to be taken. Pseudoephedrine should not be used in patients with high blood pressure.
that is severe or uncontrolled, or with severe acute or chronic kidney disease or failure. Also, health-care professionals should advise patients to stop using these medicines immediately and seek treatment if they develop symptoms of PRES and RCVS such as severe headache with a sudden onset, feeling sick, vomiting, confusion, seizures and visual disturbances.

Reference:
Patients and carers, EMA, 1 December 2023 and 26 January 2024 (link1 and link2 to the source within www.ema.europa.eu)
(See also WHO Pharmaceuticals Newsletter No.2, 2023: Pseudoephedrine and Risks of PRES and RCVS in Europe)

Statins

Potential risk of myasthenia gravis and ocular myasthenia gravis

United Kingdom. The MHRA has announced that the product information for all statins is being updated to list myasthenia gravis and ocular myasthenia gravis as adverse drug reactions.

Statins are indicated for the treatment of atherosclerotic cardiovascular disease through lowering the level of low-density lipoprotein (LDL) cholesterol in the blood. Currently available statins in the UK are atorvastatin, fluvastatin, pravastatin, rosuvastatin and simvastatin.

Globally, there has been a very small number of reports of new-onset or aggravation of pre-existing myasthenia gravis with statins. A recent European review recommended new warnings on the risk of new onset or aggravation of pre-existing myasthenia gravis with multiple statins. The findings of this review were considered by the Pharmacovigilance Expert Advisory Committee (PEAG) of the CHM, which agreed with the recommendations.

Health-care professionals should advise patients taking statins to consult their doctor if they experience weakness in the arms or legs that worsens after periods of activity, double vision or drooping of eyelids, difficulty swallowing, or shortness of breath.

Reference:
Drug Safety Update, MHRA, 26 September 2023 (link to the source within www.gov.uk/mhra)
(See also WHO Pharmaceuticals Newsletter No.2, 2023: Statins and Potential risks of myasthenia gravis and ocular myasthenia in Europe)

Topiramate

Risk of neurodevelopmental disorders in children exposed in-utero

Europe. The PRAC of the EMA has recommended new measures to avoid exposure of children to topiramate in the womb due to the increased risk of neurodevelopmental disorders after exposure during pregnancy.

Topiramate is indicated for the treatment of epilepsy and prevention of migraine. Topiramate is already known to cause serious birth defects when used during pregnancy. Its use for prevention of migraine during pregnancy is already contraindicated.

The PRAC reviewed three recent observational studies. Two of these studies, which used largely the same datasets, suggest that children born to mothers with epilepsy and who were exposed to topiramate in the womb may have a two- to three-fold higher risk of neurodevelopmental disorders, in particular autism spectrum disorders, intellectual disability or attention deficit hyperactivity disorder (ADHD), compared with children born to mothers with epilepsy not taking antiepileptic medication. The third study did not show an increased risk of these outcomes.

The PRAC recommends that the medicine should not be used for the treatment of epilepsy during pregnancy unless there is no other suitable treatment available. The PRAC also recommends additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb. The programme includes the following measures:

• a pregnancy test before starting treatment;
• counselling about the
Regulatory matters

- risks of topiramate treatment and the need for highly effective contraception throughout treatment;
- a review of ongoing treatment at least annually by completion of a risk awareness form;
- topiramate treatment of patients of childbearing potential initiated and supervised by a physician experienced in the management of epilepsy or migraine.

These measures will inform any woman or girl who is able to have children of the risks of taking topiramate during pregnancy and the need to avoid becoming pregnant while taking topiramate.

Reference:
Patients and carers, EMA, 1 September 2023 (link1 and link2 to the source within www.ema.europa.eu)
(See also WHO Pharmaceuticals Newsletter No. 4, 2023: Topiramate and Risk of neurodevelopmental disorders in children exposed in- utero in New Zealand and Australia, No.3, 2022 in Europe)

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
**Baclofen**

**Risk of overdose on off-label use**

**Australia.** The Therapeutic Goods Administration (TGA) has alerted health-care professionals on the risk of overdose of baclofen tablet form, particularly when baclofen is used off-label at higher doses for the treatment of alcohol-use disorder. Recent coronial inquiries into two deaths have highlighted the need for this alert.

Baclofen is GABA agonist and is indicated for the suppression of voluntary muscle spasm in multiple sclerosis and spinal lesions. The product information for baclofen includes warnings about the risk of suicide and suicide-related events, recommending close supervision of patients with alcohol-use disorder, depression and/or a history of previous suicide attempts.

The optimum dosage listed in the product information ranges from 30 to 75 mg daily, although occasionally doses up to 100 mg daily may be necessary in hospitalised patients. Higher dosages may be prescribed for off-label use in treating alcohol-use disorder. Close supervision of patients being treated with baclofen who have depression or a history of previous suicide attempts is recommended.

**Reference:**
Safety updates, TGA, 19 October 2023 (link to the source within www.tga.gov.au)

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**Dimethyl fumarate**

**Potential risk of Fanconi syndrome not supported**

**Canada.** Health Canada’s review did not find sufficient evidence to support a potential risk of Fanconi syndrome (a syndrome of inadequate reabsorption in the proximal renal tubules of the kidney) with use of dimethyl fumarate.

Dimethyl fumarate is indicated for the treatment of adult patients with a form of multiple sclerosis.

Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, and scientific literature. As a result, sufficient evidence to support a link between the risk of Fanconi syndrome and the use of dimethyl fumarate for the treatment of multiple sclerosis was not found.

The safety review was triggered by a labelling update for dimethyl fumarate-containing products by the EMA. Fanconi syndrome was reported in Europe for a product containing dimethyl fumarate in combination with other fumaric acid esters used to treat psoriasis. On the other hand, in Canada, dimethyl fumarate is not authorized for the treatment of psoriasis. In addition, only single ingredient dimethyl fumarate, and not fumaric acid ester compounds, is authorized in Canada.

**Reference:**
Health Product InfoWatch, Health Canada, November 2023 (link to the source within www.hc-sc.gc.ca)

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**Fluoroquinolone antibiotics**

**1. Risk of suicidal thoughts and behaviour**

**United Kingdom.** The MHRA has reminded health-care professionals to be alert to the risk of psychiatric reactions, including depression and psychotic reactions, which may potentially lead to thoughts of suicide or suicide attempts. The MHRA has received a coroner’s report following the death of a patient who died by suicide after being treated with ciprofloxacin.

Warnings on the potential for psychiatric adverse drug reactions to occur with ciprofloxacin and other fluoroquinolones are included in the product information. In rare cases, depression or psychosis can progress to suicidal ideation or suicide attempts. If this happens, ciprofloxacin should be discontinued immediately. Health-care professionals are also reminded to advise patients to be alert to these risks.

**Reference:**
Drug Safety Update, MHRA, 26 September 2023 (link to the source within www.gov.uk/mhra)

(See also WHO Pharmaceuticals Newsletter No. 6, 2019: Fluoroquinolones and Risk of psychiatric symptoms in Japan)
2. Risks of persisting serious adverse reactions

New Zealand. The Medsafe has alerted healthcare professionals on the risks of prolonged, disabling and potentially irreversible serious adverse reactions including tendonitis and tendon rupture, and peripheral neuropathy associated with use of fluoroquinolone antibiotics (ciprofloxacin, moxifloxacin, and norfloxacin are currently available in New Zealand).

Healthcare professionals should inform patients about the risks associated with fluoroquinolones and advise them to tell their doctor straight away if symptoms develop. Discontinuing fluoroquinolone treatment may reduce the risk of irreversible adverse reactions.

Reference: Prescriber Update, Medsafe, September April 2023 (link to the source within www.medsafe.govt.nz)

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

1. Potential risk of thyroid cancer not supported

Europe. The PRAC of the EMA has concluded that the available evidence does not support a causal association between the Glucagon-Like Peptide-1 Receptor Agonists (GLP-1) - exenatide, liraglutide, dulaglutide, semaglutide, and lixisenatide - and cancer of the thyroid.

GLP-1 receptor agonists are used to treat type 2 diabetes and, in some cases, for the treatment of obesity and overweight under certain conditions.

The PRAC reviewed evidence from observational studies as well as cumulative data submitted by the marketing authorisation holders (MAHs). At present, the PRAC considers that no updates to the product information are warranted based on the available data.

Reference: Patients and carers, EMA, 27 October 2023 (link to the source within www.ema.europa.eu)

2. Potential risk of suicidal thoughts and thoughts of self-harm

Europe. The PRAC is reviewing data on the risk of suicidal thoughts and thoughts of self-harm with GLP-1 receptor agonists.

The review was triggered by the Icelandic medicines agency following reports of suicidal thoughts and self-injury in people using liraglutide and semaglutide medicines. It is not yet clear whether the reported cases are linked to the medicines themselves or to the patients’ underlying conditions or other factors. The PRAC has agreed further lists of questions to be addressed by the respective MAHs for these medicines and will rediscuss this topic at its meeting in April 2024.

Reference: Patients and carers, EMA, 11 July & 1 December 2023 (link1 and link2 to the source within www.ema.europa.eu)

United States. The US FDA has been evaluating reports of suicidal thoughts or actions in patients treated with GLP-1 receptor agonists. The US FDA’s preliminary evaluation has not found evidence that use of these medicines causes suicidal thoughts or actions. The US FDA will communicate final conclusions and recommendations after completion of the review or when there is more information to share.

Reference: MedWatch, US FDA, 11 January 2024 (link to the source within www.fda.gov)

3. Potential risk of hypoglycaemia from falsified products containing insulin

United Kingdom. The MHRA has asked healthcare professionals to remain vigilant for symptoms linked to hypoglycaemia in patients who may have obtained falsified GLP-1 receptor agonist products and provide appropriate treatment for any patient who may have inadvertently administered insulin via these products. In the UK, falsified GLP-1 receptor agonist products have been found, including...
Mefenamic acid is a nonsteroidal anti-inflammatory drug (NSAID) and is indicated for the treatment of mild to moderate pain, inflammation, fever, and dental pain.

Health-care Professionals, and patients are advised to closely monitor the possibility of DRESS associated with mefenamic acid and to report to the IPC if suspected event is occurred.

Reference:
Drug Safety Update, MHRA, 23 November 2023 (link to the source within www.gov.uk/mhra)

Mefenamic acid

Potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS)

India. The Indian Pharmacopoeia Commission (IPC) has announced that its preliminary analysis of the Pharmacovigilance Programme of India (PvPI) database has found a potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS) associated with use of mefenamic acid.

Proton Pump Inhibitors (PPIs)

Risk of acute tubulointerstitial nephritis (TIN)

South Africa. The South African Health Products Regulatory Authority (SAHPRA) has alerted health-care professionals on the risk of acute tubulointerstitial nephritis (TIN) associated with use of Proton Pump Inhibitors (PPIs: pantoprazole, dexlansoprazole, esomeprazole, and rabeprazole). TIN (previously called interstitial nephritis) is characterized by an inflammatory reaction within the tubulointerstitial space of the kidney, and acute TIN can result in acute kidney injury. Symptoms and signs of acute TIN may be nonspecific and are often absent unless symptoms and signs of renal failure develop. Many patients develop polyuria (increased frequency of urination) and nocturia (the need for patients to get up at night on a regular basis to urinate).

Health-care professionals are advised that treatment by PPIs must be stopped when TIN is suspected; PPIs are contraindicated in patients who previously experienced TIN while on treatment with PPIs; and patients should be asked to report any alteration in urine volumes or if they suspect that there is blood in their urine while on PPIs.

Reference:
Safety Information and Updates, SAHPRA, 30 October 2023 (link to the source within www.sahpra.org.za)
Summary and recommendations from the third joint meeting of the
WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
and WHO Global Advisory Committee on Vaccine Safety (GACVS)

13-15 November 2023

The third joint meeting of the WHO Advisory Committee of Medicinal Products (ACSoMP) and WHO Global Advisory Committee on Vaccine Safety (GACVS) occurred between the 13 to 15 November 2023 at WHO Headquarters in Geneva, Switzerland. The two advisory Committees meet twice a year, in May (independently) and in November (jointly). A summary of the discussions and recommendations from the medicines-specific sessions and from sessions of common interest for the pharmacovigilance of both medicines and vaccines is provided below. The medicines-specific sessions were chaired by Dr Gerald Dal Pan from the United States Food and Drug Administration (US FDA) and sessions common to both vaccines and medicines were co-chaired by Dr Dure Samin Akram from the Health, Education and Literacy Program in Pakistan, Dr Rita Helfand, Centre of Disease Control (CDC), United States and Dr Gerald Dal Pan.

Update on Cohort Event Monitoring (CEM) project and implementation in pandemic response

Active surveillance for COVID-19 therapeutics (molnupiravir and nirmatrelvir-ritonavir) has been discussed in previous ACSoMP meetings. The objective of the session was to update the Committees on work done to leverage lessons learned with CEM to better prepare for future pandemics. The committees were updated on progress of the WHO-coordinated CEM study for COVID-19 therapeutics. Two of the four countries that expressed interest are currently collecting data. The number of patients recruited is limited due to the drop in usage. The plan to conduct a survey for lessons learned was shared. The objective is to understand the challenges and successes, identify gaps in infrastructure, processes and capacity needed to perform active surveillance, and use findings to develop recommendations for preparedness. The Ghana FDA also shared their experience of conducting active surveillance which was used during the COVID-19 pandemic to compliment existing spontaneous reporting systems.

Key lessons learned for success included collaboration with the expanded programme of immunization (EPI), involvement of regional level at planning stages, involvement of National Service staff as the study team members, and making participants feel cared for through the follow up process leading to more willingness to share information.

Discussion and Recommendations:
The Committees welcomed the concept of the study and the aspiration to implement a CEM and asked to be kept informed of progress and results.

Safety issues due to administration errors of medicines and vaccines

The objective of the session was to provide updates on safety issues related to medication and immunization errors. The WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre (UMC) provided an overview of reports of medication errors in VigiBase (the WHO global database of Individual Case Safety Reports). Using "medication error" as the search term (October 2023), there were more than 1.5 million cases of medication errors reported in VigiBase, with 78% medicines and 22% vaccines. General characteristics such as top reporting countries, reporters, products with the most frequent reports, proportion of reports in males and females, and different age groups were described.

1 https://cdn.who.int/media/docs/default-source/pvg/acsomp/acsomp-composition.pdf?sfvrsn=7c4030da_2 (accessed January 2024)
3 A summary from the vaccine specific sessions is published on WER: Weekly Epidemiological Record 99 (09), 95 - 103. World Health Organization
https://iris.wto.int/handle/10665/376151 (accessed March 2024)
4 ACSoMP recommendations May 2023 https://cdn.who.int/media/docs/default-source/pvg/2023-may-acsomp_recommendations.pdf?sfvrsn=5d389433_1&download=true (accessed January 2024)
5 ACSoMP recommendations December 2022 https://www.who.int/publications/m/item/2022-december-acsomp-recommendations (accessed January 2024)
6 ACSoMP recommendations June 2022 https://www.who.int/publications/m/item/2022-acsomp-recommendations (accessed January 2024)
The Committees were briefed on the third WHO Global Patient Challenge- Medication Without Harm, which began in 2017. WHO commissioned a meta-analysis to investigate the preventable burden of medication-related harm. A draft report has been developed, and initial findings show that one in 20 patients is impacted by an avoidable medication-related harm. Globally, the pooled prevalence is around 5%, (7% in lower- and middle-income countries, and 4% in high-income countries). Approximately, 25% of these are life-threatening. The aim of the Challenge is to reduce severe avoidable harm related to medications by 50% globally.

**Discussion and Recommendations**

The Committees recognized that the opportunity should be taken to conduct further analysis of reports in VigiBase to determine the magnitude of adverse events. An in-depth analysis of each medication error report would be required to fully understand how the error occurred. The Committee welcomed the initiative of the third WHO Patient Safety Challenge, "Medication Without Harm", and discussed the overlap of nomenclature between drug-related problems, preventable adverse drug reactions, and medication errors. It is important that there is more clarity around definitions to ease reporting.

**ADR Reporting**

The objective of the session was to share updated core variables and present WHO standard form for suspected ADR Reporting and solicit feedback. The core variables comprise of 35 variables, divided into six sections: record identifier, patient identification, suspected adverse drug reaction(s)/details, drug(s)/details, past medical history and any other relevant information, reporter’s information. The Scope of the core variables is primarily for signal detection, where further investigation of individual case causality assessment is needed. The main aim of the core variables is to support standardization of the information transmitted to the WHO global database of Individual Case Safety Reports, VigiBase and to improve causality assessment, assessment of seriousness and preventability.

**Discussion and Recommendations:**

ACSoMP acknowledged the benefit gained through updating the 35 core variables. The potential of their incorporation into national reporting systems means increasing universality of data acquired through the use of Vigi-tools and aligning the data being sought in VigiFlow and VigiBase with the data being captured at point of care. The Committee mentioned that there needs to be a balance between thoroughness and the time needed to complete a report. Additionally, narratives are very important and help with the analytical tools. Consideration must be given to clearly communicate and explain the updated core variables, its intent and purpose at the time of the rollout.

**Update on Miltefosine and WHO procedure for addressing signals**

The object of the session was to provide updates on actions taken to minimize risk of ocular adverse events with the use of miltefosine. This topic has been discussed in previous ACSoMP meetings. In December 2022, ACSoMP supported the conclusions of the multidisciplinary technical group (MTG) which were published by WHO together with further documents to minimize the risks. In May 2023, ACSoMP discussed lessons-learned and reviewed a patient information brochure, which has since been finalized. A public assessment report is being finalized and a publication of a peer review article is planned. An update of new cases was presented by UMC. It was not known whether the recommended risk minimization measures were implemented in the cases that occurred after the publication of ACSoMP’s recommendations in December 2022. An outline of a WHO procedure for addressing future signals was presented to the Committee.

**Discussion and recommendations**

The Committee discussed the process of managing new signals and how the decision to engage ACSoMP is made. A standard operating procedure for addressing signals is essential and will ensure a timely response to identified signals. The use of follow up forms to obtain further information on cases to aid signal detections was suggested. The importance of access to the narrative in reports for signal detection was highlighted, and challenges of sharing of information such as the narrative globally, was suggested as an agenda item in future ACSoMP meetings.

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7 WHO Measures to minimize the risk of ocular adverse events with miltefosine [website]. (https://www.who.int/news/item/12-04-2023-acsom-p-miltefosine accessed January 2024)
Feature

Update on Safety monitoring of Dolutegravir and Cabotegravir
The object of the meeting was to provide an update on WHO guidelines and safety monitoring of Cabotegravir (CAB LA) and Dolutegravir (DTG).

Information from a number of relevant randomized control trials were shared. The data, continues to show that DTG is highly effective and safe in pregnant women. Moreover, adverse pregnancy outcomes are not higher with preconception administration of DTG. This suggests that the neural tube defects signal on the relatively small number of exposures was erroneous and corrected with increased number of exposures. Regarding CAB LA, initial studies show the drug as being well-tolerated and there are 34 implementation studies, of which one is complete, 10 are ongoing, and 23 are planned.

The Committees were briefed on a novel collaborative approach to monitoring safety of antiretrovirals in pregnancy, including surveillance. The process involves developing key principles drawing on lessons learned from past practices. There is a recognition that no one region will have enough numbers of pregnancy outcomes to answer the full scope of the safety outcomes. Work on monitoring the CAB LA studies is ongoing and WHO will continue to inform ACSoMP. The Committees were also informed of ongoing joint assessment activities involving several WHO units that aim to promote collaboration amongst national authorities for facilitated registration of quality assured products.

Discussion and recommendations
The Committees recognized the importance of international collaboration in pregnancy related research, and the Dolutegravir story is a good example of how careful follow up can clarify a signal in a beneficial way.

The Committee welcomes the new approach to the study of HIV and pregnancy, and acknowledges the opportunity for WHO HIV, Pharmacovigilance (PVG) and Facilitated Product Introduction (FPI) teams to work together on this issue.

Sodium valproate safety updates
The objective of the session was to provide updates on actions taken since the previous ACSOmp meeting\(^3\). The Committee was informed of the release date (20 November 2023) of the 3rd edition of the WHO Mental Health GAP Action (updated mhGAP) guideline. The updated guideline includes recommendations on the use of sodium valproate in the treatment of epilepsy and bipolar disorder. This is available on the WHO website.\(^8\)

The dissemination of information on the third edition of the mhGAP guideline is occurring through various platforms and channels, including an article in *Lancet Psychiatry*\(^9\), WHO websites\(^10\), press briefings, and social media.

Furthermore, the Committee was briefed on a post-authorization study on outcomes of paternal exposure to sodium valproate required by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA. The study is designed as a retrospective, non-interventional longitudinal population-based cohort with secondary data derived from multiple registry databases.

Discussions and recommendations
The Committees welcomed the work done to support the drafting of a new WHO guideline regarding the use of Valproic acid, and it awaits the result of the assessment by the European Medicine Agency currently ongoing.

Upcoming ACoMP meetings
The next ACoMP meeting is planned to be a virtual meeting in May 2024, with a joint ACoMP/GACVS in-person/hybrid meeting in November 2024.

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8 Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders [https://www.who.int/publications/i/item/9789240084278](https://www.who.int/publications/i/item/9789240084278) (accessed January 2024).

9 Reducing the uses of valproate: a controversial decision; The Lancet Neurology (February 2024) DOI: [https://doi.org/10.1016/S1474-4422(23)00507-0](https://doi.org/10.1016/S1474-4422(23)00507-0).
