WHO pharmaceuticals NEWSLETTER

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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 the meeting report of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), 13-14 May 2024.

Contents

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Contents

Regulatory matters

Safety of medicinal products

Feature

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

Azithromycin

Rare risk of cardiovascular death

Australia. The Therapeutic Goods Administration (TGA) has updated warning about the risk of sudden cardiovascular death to the Product Information (PI) and Consumer Medicine Information (CMI) documents for azithromycin.

Azithromycin is indicated for mild to moderate infections in adults, including upper and lower respiratory tract infections, as well as uncomplicated skin and skin structure infections, among others.

Azithromycin already carried a warning of ventricular arrhythmias associated with prolonged QT interval. The update describes an increased short-term risk of cardiovascular death with azithromycin compared to other antibacterial drugs, including amoxicillin. This risk is rare but appears to be greater during the first 5 days of azithromycin use.

The new warning also advises that healthcare professionals should consider a screening ECG in patients at high risk of a prolonged QT, based on their medical history or ongoing medical treatments.

The update was made following a recommendation from the Australian Advisory Committee on Medicines. This was based on the Committee's review of published literature including observational studies, the seriousness of the adverse event and updated warnings by the Food and Drug Administration in the US.

It is important to note that the Committee observed that the information in the observational studies was insufficient to establish or exclude a causal relationship between acute cardiovascular death and azithromycin use due to inconsistent results between studies.

Reference:

Safety updates, TGA, 1 August 2024 (link to the source within www.tga.gov.au)

(See also WHO pharmaceuticals newsletter No.4, 2023: Azithromycin and Risk of fatal heart rhythms)

Chimeric antigen receptor (CAR) T cell immunotherapies

1. Modification of risk evaluation and mitigation strategies (REMS)

United States. The US Food and Drug Administration (FDA) has determined that the approved risk evaluation and mitigation strategies (REMS) for CAR T cell immunotherapies (Chimeric antigen receptor (CAR) T-cell therapy) must be modified to minimize the burden of complying with the REMS on the healthcare delivery system.

CAR T cell immunotherapies are human gene therapy products in which the T cell specificity is genetically modified to enable recognition of a desired target antigen for therapeutic purposes. A REMS is a safety program that US FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. Because of the risks of cytokine release syndrome (CRS) and neurological toxicities, the following currently approved BCMA- or CD19-directed autologous CAR T cell immunotherapies are available only through a restricted program under a REMS: idecabtagene vicleucel (Abecma®), lisocabtagene maraleucel (Breyanzi®), ciltacabtagene autoleucel (Carvykti®), tisagenlecleucel (Kymriah®), brexucabtagene autoleucel (Tecartus®) and axicabtagene ciloleucel (Yescarta®).

US FDA concluded, information regarding the risks for CAR T cell immunotherapies can be conveyed adequately via the current product labelling, which includes a boxed warning for the risks of CRS and neurological toxicities, and the Medication Guides which are a part of the approved labelling. Thus, the REMS have been modified to remove requirements for educational and training materials. Additionally, the requirement to report adverse events suggestive of CRS or neurological toxicities to the REMS has been removed. Adverse event reporting requirements in accordance with the Code of Federal Regulations (CFR) are adequate for continued routine safety monitoring for these products.

The goal of the modified

REMS is to mitigate the risks of CRS and neurological toxicities by ensuring that hospitals and their associated clinics that dispense the above products are specially certified and have on-site, immediate access to tocilizumab. The REMS for each product requires that a minimum of two doses of tocilizumab must be available on-site for each patient before infusion of the CAR T cell immunotherapy. Tocilizumab is approved for use in adults and pediatric patients aged 2 years and older with CAR T cell-induced severe or life-threatening cytokine release syndrome and other related syndromes.

Reference:
Safety & availability (biologics), US FDA, 26 June 2024 (link to the source within www.fda.gov)

(See also WHO pharmaceuticals newsletter No.4, 2024: CAR T cell immunotherapies and Risk of T-cell malignancy)

2. Risk of secondary malignancies of T-cell origin

Europe. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has concluded that secondary malignancies of T-cell origin may occur after treatment with chimeric antigen receptor (CAR) T-cell medicines.

CAR T-cell medicines belong to a type of personalised cancer immunotherapies where one type of a patient's white blood cells (T-cells) are reprogrammed and reinjected to attack the cancer.

The PRAC evaluated data on 38 cases of secondary malignancy of T-cell origin, including T-cell lymphoma and leukaemia, reported among approximately 42,500 patients who have been treated with CAR T-cell medicines. Tissue samples were tested in half of the cases, revealing the presence of the CAR construct in 7 cases. This suggests that the CAR T-cell medicine was involved in disease development. The secondary malignancies of T-cell origin have been reported within weeks and up to several years following administration of CAR T-cell medicines. Patients treated with these medicines should be monitored life-long for new malignancies.

Since approval of CAR T-cell medicines, the product information has advised that patients treated with these products may develop secondary malignancies. The product information and the risk management plans will be updated to include the new information concerning secondary malignancy of T-cell origin.

Reference:
News, EMA, 14 June 2024 (link to the source within www.ema.europa.eu)

Fezolinetant

Risk of liver injury

United States. The US FDA has added a warning about the risk of liver injury to the existing warning about elevated liver function test values and required liver function testing in the prescribing information for fezolinetant (Veozah®).

Fezolinetant is a nonhormonal prescription medicine approved to reduce the frequency and severity of moderate to severe hot flashes caused by menopause. The medicine is in a drug class called neurokinin 3 (NK3) receptor antagonists. It works to restore the balance between estrogen hormones and a brain chemical called neurokinin B (NKB) by blocking the activities of the NK3 receptor, which plays a role in the brain's control of body temperature.

The FDA made this update after reviewing a post marketing report of a patient with elevated liver function test values and signs and symptoms of liver injury after taking the medicine for about 40 days. The FDA also added new recommendations for patients and health care professionals about increasing the frequency of liver function testing, adding monthly testing for the next 2 months after starting fezolinetant, and then at months 3, 6, and 9 of treatment as already recommended. The updated prescribing information also instructs patients to stop the medicine immediately and contact the health care professional who prescribed the medicine if signs and symptoms of liver injury occur.

Reference:
MedWatch, FDA, 12 September 2024 (link to the

source within www.fda.gov)

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

Risk of aspiration and aspiration pneumonia during general anaesthesia or deep sedation supported

Europe. The PRAC of the EMA has recommended new measures to minimise the risk of aspiration and aspiration pneumonia reported in patients taking glucagon-like peptide-1 receptor agonists (GLP-1 RAs) who undergo surgery with general anaesthesia or deep sedation. Aspiration and aspiration pneumonia can be caused by accidentally inhaling food or liquid into an airway instead of swallowing it through the oesophagus. It can also occur when stomach content goes back into the throat.

GLP-1 RAs are medicines used for treatment of type 2 diabetes and obesity. As part of their action, GLP-1 RAs slow down gastric emptying and there is a biologically plausible increased risk for aspiration in association with anaesthesia and deep sedation when taking these medicines. Delayed gastric emptying is already listed in the product information for the different GLP-1 RAs: dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide and tirzepatide.

The PRAC reviewed available data including case reports in EudraVigilance, scientific literature and clinical and non-clinical data submitted by the marketing authorisation holders for these medicines. The committee could not establish a causal association between GLP-1 analogues and aspiration, but because of the known action of delayed gastric emptying and the presence of clinical trial cases and post marketing cases, the PRAC considered that healthcare professionals and patients should be informed on this potential consequence of delayed gastric emptying.

Therefore, the PRAC has recommended that the risk of residual gastric content being present because of delayed gastric emptying should be considered before performing procedures with general anaesthesia or deep sedation. The product information of GLP-1 RAs will be updated accordingly, including a warning to patients that they should inform the doctor involved if they take these medicines and are scheduled to undergo surgery under anaesthesia or deep sedation.

Reference:
News, EMA, 12 July 2024 (link to the source within www.ema.europa.eu)

Promethazine (oral)

Risk of psychiatric and central nervous system side effects

New Zealand. The Medsafe has announced that promethazine (oral) products are now contraindicated in children under 6 years of age due to the risk of psychiatric and central nervous system side effects.

Promethazine is a sedating antihistamine. Medicines containing promethazine may be used to treat allergies (including hay fever) and nausea and vomiting (including travel sickness) in children aged 6 years and older.

Promethazine was already contraindicated in children under 2 years of age due to the risk of fatal respiratory depression (breathing difficulties).

This change follows a safety review by Sanofi, the manufacturer of makes medicines containing promethazine, identified a high risk of psychiatric and central nervous system side effects related to promethazine use in children aged between 2 and 5 years. In addition to known side effects, children under 6 years of age experienced psychomotor hyperactivity, aggression and hallucinations. At high doses, promethazine caused learning and understanding difficulties.

Reference:
Safety information, Medsafe, 13 May 2024 (link to the source within www.medsafe.govt.nz)

Preparations containing brimonidine tartrate

Risks of serious corneal opacity

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the

Pharmaceuticals and Medical Devices Agency (PMDA) have issued a notification instructing the marketing authorization holders (MAHs) to revise PRECAUTIONS on the package insert of the preparations containing brimonidine tartrate to include risk of serious corneal opacity.

Preparations containing brimonidine tartrate include brimonidine tartrate, brimonidine tartrate/timolol maleate, brimonidine tartrate/brinzolamide, and ripasudil hydrochloride hydrate/brimonidine tartrate, which are used for the treatment of glaucoma and ocular hypertension in patients who have not responded sufficiently to other anti-glaucoma drugs.

The MHLW and PMDA received a total of 19 cases, of which 11 cases have been confirmed where a causal relationship between the preparations containing brimonidine tartrate and the event was reasonably possible.

In addition, among cases of serious corneal opacity, especially for the cases in which corneal opacity spread from the peripheral part of the cornea to the central part in a fan-like pattern developing into the central part of the cornea (pupillary area), it is known that the opacity part becomes scarred even after discontinuation of the preparations, resulting in poor visual prognosis. Special attention should be paid to these cases. If corneal infiltration or corneal neovascularisation is observed as a prodromal symptom, it is important to discontinue administration of the preparations and to administer steroid eye drops at that time. Therefore, ophthalmologists must monitor the presence or absence of findings such as corneal infiltration or corneal neovascularisation through periodic medical examinations. If any findings of prodromal symptoms or corneal opacity are observed, ophthalmologists are encouraged to take appropriate measures.

Reference:
Pharmaceuticals and Medical Devices Safety Information, MHLW/PMDA, July 2024 (link to the source within www.pmda.go.jp/english/)

Topiramate

Introduction of new safety measures

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has concluded that topiramate is now contraindicated in pregnancy and in women of childbearing potential unless the conditions of a Pregnancy Prevention Programme are fulfilled.

Topiramate is indicated for the prophylaxis of migraine and for the treatment of epilepsy. It is available as tablets, a liquid oral solution and as capsules that can be swallowed whole or sprinkled on soft food.

Following a comprehensive review of the safety of antiseizure medications in pregnancy, including topiramate, MHRA concluded that the use of topiramate during pregnancy is associated with significant harm to the unborn child (both from the confirmed risks of congenital malformations and low birth weight and the potential risk of neurodevelopmental disorders). As a result, new restrictions are being introduced. Topiramate is now contraindicated in women of childbearing potential unless they meet the conditions of the Pregnancy Prevention Programme (for all indications), during pregnancy for migraine prophylaxis, and during pregnancy for epilepsy unless no other suitable treatment is available.

Reference:
Drug Safety Update, MHRA, 20 June 2024 (link to the source within www.gov.uk/mhra)
(See also WHO pharmaceuticals newsletter No.2, 2024: Topiramate and Risk of neurodevelopmental disorders in children exposed in-utero)

Aciclovir and valaciclovir-containing medicines

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

South Africa. The South African Health Products Regulatory Authority (SAHPRA) has informed healthcare professionals about the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) associated with the use of aciclovir and valaciclovir-containing medicines.

Aciclovir is indicated for the treatment of initial and recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes simplex virus infections, in both immunocompetent and immunocompromised patients. It is also indicated for the treatment of herpes zoster (shingles) if the lesions are not older than 72 hours, as well as other related syndromes. Valaciclovir, the L-valine ester of aciclovir, is indicated for the treatment of herpes zoster (shingles), the episodic treatment of recurrent genital herpes in immunocompetent adult patients, and other related syndromes.

DRESS also known as drug induced hypersensitivity syndrome (DIHS), is a rare, but serious, and potentially life-threatening fatal drug reaction, characterised by symptoms which include widespread rash, high body temperature, liver enzyme elevations, elevated white blood cell count (including eosinophils), enlarged lymph nodes and possibly other body organs involvement. The symptoms of DRESS typically appear within 2 weeks to 2 months after starting treatment with aciclovir- or valaciclovir-containing medicines.

The available data from literature and post marketing reports provide sufficient evidence that corroborates the association of aciclovir- and valaciclovir-containing medicines, and the risk of DRESS.

Reference:
Communication To Health Care Professionals, SAHPRA, 8 July 2024 (link to the source within www.sahpra.org.za)

Eribulin mesylate

Risk of teratogenicity and other reproductive adverse events

South Africa. The SAHPRA has reminded health-care professionals about the risk of teratogenicity and other reproductive adverse events associated with the use of eribulin mesylate (Halaven®).

Eribulin mesylate is a genotoxic anticancer medicine indicated for the treatment of adult patients with locally advanced or metastatic breast cancer who have progressed after at least one chemotherapeutic regimen for advanced disease.

Eribulin mesylate is also indicated for the treatment of adult patients with unresectable liposarcoma who have received prior anthracycline containing therapy (unless unsuitable) for advanced or metastatic disease.

The SAHPRA has advised health-care professionals that eribulin mesylate may cause teratogenicity and other reproductive adverse events (embryotoxicity, mutagenicity, spontaneous abortions and foetal deaths) due to its genotoxic nature. In males, eribulin mesylate may cause DNA damage in the sperm, potentially resulting in adverse events in the embryo or foetus of a female sexual partner. In females, eribulin mesylate may directly affect the embryo or foetus; or may cause DNA damage in the oocytes.

To minimise the risk of drug-induced heritable DNA damage and to ensure that genomic integrity of gametes at the time of conception is maintained, female patients of childbearing potential using eribulin mesylate and female sexual partners, (with childbearing potential) to male patients receiving this product are generally advised to use highly effective contraception during treatment and for an adequate period following the end of treatment.

Reference:
Communication to health care professionals, SAHPRA, 19 June 2024 (link

to the source within www.sahpra.org.za)

Glatiramer acetate

Risk of anaphylactic reactions

Europe. The PRAC of the EMA has concluded that glatiramer acetate is associated with anaphylactic reactions, which may occur shortly following administration of glatiramer acetate even after months up to years after initiation of treatment. Cases with a fatal outcome have been reported. Initial symptoms of anaphylactic reactions may overlap with symptoms of post-injection reaction and could potentially lead to a delay in the identification of an anaphylactic reaction.

Glatiramer acetate is authorized for the treatment of relapsing forms of multiple sclerosis.

The PRAC has agreed a direct healthcare professional communication (DHPC) to inform healthcare professionals about this risk and to recommend that patients and/or caregivers be advised of the signs and symptoms and to seek emergency care in the event of an anaphylactic reaction. If such a reaction occurs, treatment with glatiramer acetate must be discontinued.

Reference:
News, EMA, 12 July 2024 (link to the source within www.ema.europa.eu)

Medicines containing Garcinia gummi-gutta or hydroxycitric acid

Potential risk of rare cases of liver injury

Australia. TGA has reminded consumers and healthcare professionals that medicines and herbal supplements containing *Garcinia gummi-gutta (Garcinia cambogia)* or hydroxycitric acid (HCA) may cause liver injury in rare cases. The risk also relates to other ingredients that contain HCA: *Garcinia quaesita,* hydroxycitrate complex, calcium hydroxycitrate, sodium hydroxycitrate, or potassium hydroxycitrate.

Medicines and herbal supplements containing *Garcinia gummi-gutta* and other HCA-ingredients can be bought in supermarkets, health food shops and pharmacies without a prescription and without the advice of a health professional.

TGA has completed an investigation into the risk of liver injury for the ingredient *Garcinia gummi-gutta (Garcinia cambogia)* and its naturally occurring component HCA. Available evidence shows that there may be a rare risk of liver injury from taking *Garcinia gummi-gutta (Garcinia cambogia)* or HCA. Liver injury concerns also apply to the other HCA-containing ingredients. TGA will continue to monitor this issue and are currently considering further regulatory action.

TGA advises consumers that if you take medicines or herbal supplements containing *Garcinia*-related ingredients, you should be aware of the potential risk for liver injury. If you experience any of the following symptoms—yellowing of the skin or eyes, dark urine, nausea, vomiting, unusual tiredness, weakness, stomach or abdominal pain, or loss of appetite—you should immediately stop taking the supplement and seek medical advice.

Reference:

Safety alerts, TGA, 8 August 2024 (link to the source within www.tga.gov.au)

Medicines containing Andrographis paniculata

Potential risk of severe allergic reactions

Australia. TGA has reminded consumers and healthcare professionals that medicines containing the herb *Andrographis paniculata* (andrographis) may cause allergic reactions, including life-threatening anaphylaxis, in some individuals.

Andrographis is a widely used medicinal herb that can be bought in supermarkets, health food shops and pharmacies without a prescription.

Since 2005, TGA has received over 300 reports of anaphylaxis and/or hypersensitivity reactions to medicines containing andrographis. More than 200 of these reports have been received since 2019, including one case of a fatal anaphylactic reaction in someone who had used a medicine containing andrographis.

TGA advises consumers that if you take medicines or herbal supplements containing andrographis, you should be aware of the potential for allergic reactions. If you experience any signs of an allergic reaction, you should immediately stop using the medicine and seek medical advice.

Reference:

Safety alerts, TGA, 2 July 2024 (link to the source within www.tga.gov.au)

Naltrexone and bupropion

Risk of interactions with opioid-containing medicines

Europe. EMA recommends strengthening existing advice to minimise the risks from interactions between naltrexone/bupropion (Mysimba®) and opioid-containing medicines (including painkillers such as morphine and codeine, other opioids used during surgery, and certain medicines for cough, cold or diarrhoea).

Naltrexone/bupropion is a medicine used along with diet and exercise to help manage weight in adults who have obesity or who are overweight and have weight-related complications such as diabetes, abnormally high levels of fat in the blood, or high blood pressure.

EMA is advising that opioid painkillers may not work effectively in patients taking naltrexone/bupropion, because the active substances naltrexone blocks the effects of opioids. If a patient requires opioid treatment while taking naltrexone/bupropion, for example due to a planned surgery, they should therefore stop taking naltrexone/bupropion for at least three days before treatment with opioid medicines starts.

Furthermore, EMA is informing patients and healthcare professionals about the risk of rare but serious and potentially life-threatening reactions, such as seizures and serotonin syndrome (a potentially life-threatening condition that results from having too much serotonin in the body), in people taking naltrexone/bupropion with opioids.

To minimise these risks, EMA recommends that naltrexone/bupropion must not be used in people receiving treatment with opioid medicines. This is in addition to the existing contraindications stating that naltrexone/bupropion must not be used in people who are dependent on long-term opioids, people receiving treatment with opioid agonist such as methadone, and people going through opioid withdrawal.

Reference:
News, EMA, 26 July 2024 (link to the source within www.ema.europa.eu)

Warfarin

Risk of drug interactions with tramadol

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has reminded healthcare professionals that taking warfarin and tramadol together can cause harmful drug interactions, which can raise the International Normalised Ratio (INR), and result in severe bruising and bleeding, which in some patients could be fatal.

Warfarin is a coumarin-derived vitamin K antagonist used for prevention and treatment of blood clots. Warfarin has a low therapeutic index, which means care is required when taking co-prescribed medicines due to the possibility of interactions that could lead to an increased risk of bleeding. Tramadol is a non-selective opioid analgesic, which acts as an agonist at the mu, delta and kappa opioid receptors.

The MHRA has received a report following the death of a patient who died from a bleed on the brain,

following concurrent treatment with warfarin and tramadol.

The MHRA has advised healthcare professionals to ask patients about all the medicines that they are currently taking when prescribing warfarin, and be aware of the risk of increased INR when warfarin and tramadol are used together, with a risk of major bruising and bleeding which could be life-threatening.

Reference:
Drug Safety Update, MHRA, 20 June 2024 (link to the source within www.gov.uk/mhra)

(See also WHO pharmaceuticals newsletter No.4, 2023: Oral anticoagulants and Potential risk of anticoagulant-related nephropathy (ARN))

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

Report of the Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP), 13-14 May 2024

The Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003 to provide independent, authoritative, scientific advice to WHO on medicines safety issues of global or regional concern. ACSoMP is an independent expert advisory body that provides advice to the World Health Organization Director-General on pharmacovigilance policy and issues related to the safety and effectiveness of medicinal products. The 20th ACSoMP meeting was held virtually from 13-14 May 2024. A summary of the presentations and recommendations are provided below. The next ACSoMP meeting will be organized as a joint in-person meeting with the Global Advisory Committee on Vaccine Safety (GACVS) in Geneva and will take place in November 2024.

1. Cohort Event Monitoring of COVID-19 Therapeutics: Update and Lessons Learned
The session during the first day of the ACSoMP meeting focused on updates from Egypt on the cohort event monitoring (CEM) project for the safety of molnupiravir and on the progress of the WHO active surveillance lessons learned survey. Progress of the CEM study for molnupiravir and nirmatrelvir-ritonavir (Paxlovid) conducted by other participating countries (Jordan and Philippines) has been discussed in previous ACSoMP meetings[1,2,3]. This is the first meeting in which data from Egypt is shared.

Update on Cohort Event Monitoring of Molnupiravir in Egypt
In Egypt the CEM study of molnupiravir is conducted in 10 hospitals in five different regions across the country. Recruitment of patients started in January 2024. As of May 2024, there were 378 participants enrolled in the study. Eighty participants completed the study. The process in which the study is conducted was presented. The study has strong management processes in place and includes regular technical and administrative audits. Challenges with conducting the study include late adoption of electronic data collection tools due to security approval processes; availability of molnupiravir in hospitals; and reduced diagnosis of COVID-19 cases. The Egyptian Drug Authority presented serious adverse events and results of causality assessments to the Committee, and no concerns were identified.

WHO Active Surveillance Lessons Learned Survey: Progress and Results to Date
The WHO Pharmacovigilance team has designed a structured questionnaire-based survey to investigate challenges and successes in implementation of active surveillance during a pandemic in countries. The questionnaire is comprised of different sections related to the decision to conduct active safety surveillance, planning process, and implementation.

As of May 2024, three principal investigators in two countries have been interviewed. The target is to conduct the questionnaire-based interview in all countries that were supported by WHO to conduct active surveillance studies on COVID19 vaccines and medicines. The results of this study are expected to be published by the end of the year. Interim results were presented to the Committee. Some of the findings include the need for greater awareness of seeking ethics approval through studies through WHO and adherence to an approved protocol by WHO which can help speed up ethics approval. Special attention should be given to data collection and analysis plans (consultation with methodologists and biostatisticians is necessary). Where possible, it is preferable to recruit dedicated study staff and compensate staff for their time.

The Committee discussed the use of protocol templates and the need for design and development of protocols to start when a potential pandemic or other public health emergency starts, before medicines or vaccines are approved or in circulation. There is a need to raise the level of awareness of such studies in the general population and health care providers, and implementation could involve other stakeholders such as NGOs and health workers to facilitate a streamline process.

<u>Recommendation for active surveillance in future pandemics</u>

- Design protocols for active surveillance or cohort event monitoring with templates which can be easily customized early on, to speed up approvals at the earliest knowledge of the upcoming launch of new medicines.
- Develop guidance on communication strategy for active surveillance studies in order to enhance acceptance, engagement, and awareness of decision-makers, healthcare professionals, academics, NGOs, and the general public on the intervention.

- Considerations of different healthcare systems and health-seeking behaviours should be made in multi-country active safety surveillance studies.
- CEM is one of many active surveillance methods. The most appropriate method should be selected for a specific question and within the appropriate context (including available resources).

Recommendations for the lessons learned study

- Extend the lessons learned study to countries conducting active surveillance for products other than COVID-19 vaccines and medicines.
- Ensure the lessons learned study explores the challenges in study implementation such as limited patient enrolment, delays in approvals, and study discontinuation.

2. Update on Sodium Valproate Use and Teratogenic Concerns of Topiramate

The session during the second day of the ACSoMP meeting focused on updates on actions taken since previous ACSoMP meetings on the topics of sodium valproate use in women and girls of childbearing potential. The Committee also listened to patient groups – Independent Fetal anticonvulsant Trust (INFACT) and Fetal Anticonvulsant Syndrome association (FACSA) – on concerns of spectrum disorders associated with in utero exposure to topiramate.

Sodium Valproate safety updates

The Committee was informed of the publication of the updated Mental Health Gap Action Programme (mhGAP) Guidelines in November 2023 that target primary care providers[4]. The new WHO recommendation for women and girls who want to or may become pregnant were discussed in previous ACSoMP meetings. The development of WHO recommendations was based primarily on the results of a systematic review and network meta-analysis. Previous ACSoMP recommendations on this topic were centred around communication of the guideline update. The Committee were informed of ongoing activities towards knowledge mobilization of the guidelines, including organizing an upcoming webinar in July 2024 about this topic.

Additionally, the Committee was briefed on conclusions made by the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA on the review of a post-authorization study on outcomes of paternal exposure to sodium valproate and the risk of neurodevelopmental disorders[5]. A retrospective observational study and other sources of information including non-clinical (laboratory) studies, scientific literature and consultations with patients and clinical experts. The study data had limitations and could not establish whether the observed increased occurrence of neurodevelopmental disorders suggested by the study was due to valproate use in male patients. Nonetheless, PRAC considered precautionary measures were warranted in the interim to inform patients and healthcare professional. PRAC did not recommend limiting exposure to men under 55 but have included additional measures in the product information. This is reflected in updates to the patient information leaflet, use of a patient card, healthcare provider/patient educational material, and a direct healthcare professional communication.

The Medicines and Healthcare Products Regulatory Agency (MHRA) also updated the Committee on new safety measures introduced in January 2024 to reduce known harms from valproate, including significant risk of serious harm to baby if taken during pregnancy and the risk of impaired fertility males in the UK6. These safety measures take into account the feedback of the patients and other stakeholders on lack of awareness of risks of valproate to male reproductive health.

Recommendations

- The Committee is pleased that the previous recommendations from ACSoMP regarding valproate have been implemented. The Committee is interested in assessing the impact of the mhGAP guideline and its dissemination across different countries. An upcoming webinar will discuss this topic, and interested committee members are encouraged to join.
- The Committee will continue to monitor and follow-up and new evidence regarding the safety of valproate in males and transgenerational effects.

Teratogenic Concerns of Topiramate

The Committee listened to concerns from patient groups INFACT and FACSA, who advocate to include Fetal Topiramate Spectrum Disorder as an ICD 11 classification. INFACT liaises with clinicians in the UK, who are working on publishing data to support this request. INFACT has also commenced working with the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom in 2023 to set out a Pregnancy Prevention Program. The program requires a pregnancy test before initiation of topiramate,

discussion with the patient including risks of topiramate in pregnancy, and a strong recommendation for use of a highly effective contraception if topiramate is used. Potential steps and data required for including a term in ICD-11 were discussed. A clinical perspective of the use of topiramate in the UK was presented to the Committee by an Epileptologist. An account on how frequently it is prescribed and its place in treatment of complex epilepsy syndromes and pharmacoresistant epilepsy was described. Use of topiramate differs from that of valproate, being prescribed for more restricted indications and more severe cases of epilepsy. The need to empower patients to make informed choices was emphasized. Consideration of balancing the risk and potential harms of epilepsy treatments with benefits should be made.

Recommendations

- The Committee recommends that WHO should follow-up internally and initiate necessary steps such as performing a good quality systematic review of evidence before the application for ICD-11 coding.

WHO Survey on Drug Utilization on the Use of Sodium Valproate in LMIC

WHO presented its proposal to conduct a series of studies to better understand the use of valproate in Low- and Middle-income Countries (LMICs). Valproate is a well-established medication which was previously most commonly used antiseizure medicine for decades. Over time, studies have provided evidence of its teratogenicity. Many countries across Europe and the UK have introduced measures to reduce the use of valproate in women of childbearing potential. There is not much known about the situation in the LMICs.

The proposed series of studies will include a cross-sectional drug utilization study in LMICs (using various available data sources in 6-12 countries representing all WHO regions); a study on understanding knowledge of risks, attitudes, beliefs and behaviors (survey/ questionnaire targeting healthcare professionals and patients); a study to map the regulatory risk mitigation measures for the use of sodium valproate in women and girls of childbearing potential (cross-sectional survey of all LMIC which participate in the WHO Programme for International Monitoring); and an audit of compliance to risk mitigation measures, and impact on reducing the number of pregnancies exposed to valproate (survey of healthcare professionals and analysis of reported adverse events following foetal exposure to valproate in VigiBase before and after the introduction of risk minimisation measures).

Recommendations

- ACSoMP recommends assessing the feasibility of implementing the studies in various countries and with different data sources.
- The proposed studies on behaviors, risk minimization measures, and dissemination methods will likely be qualitative. ACSoMP suggests using web-based tools initially, followed by detailed interviews, while evaluating the feasibility of this approach.
- The studies should involve not only regulatory authorities but also academia, as well as local and regional societies.

Reference

1 ACSoMP and GACVS recommendations November 2023 (https://cdn.who.int/media/docs/default-source/medicines/pharmacovigilance/acsomp_gacvs_recomendations.pdf?sfvrsn=cf303c78_1&download=true, accessed September 2024)

2 ACSoMP recommendations May 2023 (https://cdn.who.int/media/docs/default-source/pvq/2023-may-acsomp-recommendations.pdf?sfvrsn=5d338433_1&download=true, accessed September 2024)

3 GACVS and ACSoMP recommendations December 2022 (https://cdn.who.int/media/docs/default-source/medicines/pharmacovigilance/2022-december-acsomp-recommendations.pdf?sfvrsn=a2465f84_3&download=true, accessed September 2024)

4 Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Geneva: World Health Organization; 2023. https://www.who.int/publications/i/item/9789240084278, accessed 21 November 2024)

5 Potential risk of neurodevelopmental disorders in children born to men treated with valproate medicines: PRAC recommends precautionary measures. In: European Medicines Agency /News [website]. Amsterdam: European Medicines Agency; 2024 (https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproate-medicines-prac-recommends-precautionary-measures, accessed 01 September 2024).

6 New valproate safety measures apply from 31 January. In: Government/News [website]. London: the Medicines and Healthcare products Regulatory Agency; 2024 (https://www.gov.uk/government/news/new-valproate-safety-measures-apply-from-31-january, accessed 01 September 2024).