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

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

WHO convened a hybrid meeting of ACSoMP from 11 to 12 May 2023, with some members joining in person in Geneva, and others joining online. The sessions were co-chaired by Dr. June Raine from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and Dr. Gerald Dal Pan from the United States Food and Drug Administration (US FDA). A summary of the presentations and recommendations from the meeting is provided below.

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

Molnupiravir and nirmatrelvir-ritonavir have recently been authorized for the treatment of non-severe COVID-19 disease. However, there are limited data on their safety, particularly in low- and middle-income countries (LMICs). The WHO living guideline published in July 2022 made a conditional recommendation for molnupiravir and a strong recommendation for nirmatrelvir/ritonavir in patients with non-severe COVID-19 disease with the highest risk of hospitalization[1] and recommended the implementation of a robust active surveillance programme because of safety data gaps and concerns.

WHO has developed a protocol for cohort event monitoring (CEM)[2], to support the active surveillance of molnupiravir. This protocol has been updated to include nirmatrelvir/ritonavir. The primary objectives are to characterize and estimate the incidence of all adverse events (AEs), including serious AEs, medication errors, off-label use, and misuse.

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

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

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

[2] WHO Safety monitoring of molnupiravir for treatment of mild to moderate COVID-19 infection in low and middle-income countries using cohort event monitoring: a WHO study. https://www.who.int/publications/i/item/WHO-2019-nCoV-Therapeutics-safety_monitoring-molnupiravir-2022.1

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

- In Jordan, CEM was initiated in March 2023 in six sites. However, molnupiravir has not been administered yet and nirmatrelvir-ritonavir is only available at three sites.
- In Egypt, CEM will be carried out in 10 sites once national security approval is obtained. WHO electronic tools will be used for data collection. Two variables have been added to the protocol to improve traceability: the marketing authorization holder (MAH) and the drug batch number, as there are 24 registered generic molnupiravir products.
- In the Philippines, molnupiravir is a prescription-only medication, available in pharmacies and hospitals. CEM, which will be conducted in collaboration with the Philippine College of Physicians in 25 hospitals, has just received approval from the ethics committee. Data will be collected using WHO electronic tools and paper-based diaries.
- In Bangladesh, there are 10 registered molnupiravir products available in pharmacies and hospitals without prescription. CEM will be conducted in 10 to 15 hospitals and will be run by a Clinical Research Organization (CRO). Data will be collected using the WHO electronic tools and on paper.
- In the Pan American Region, the CEM protocol has been adapted to produce two protocols tailored to the specific safety issues associated with molnupiravir and with nirmatrelvir-ritonavir. Both CEMs aim to minimize risks by promoting the rational use of these medicines, advising against the use of molnupiravir during pregnancy and highlighting the potential for drug-drug interactions with nirmatrelvir-ritonavir. Patients will be enrolled in community pharmacies that dispense the medicines prescribed in general practice. Both country-specific and pooled analyses of data from multiple countries are planned.

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

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

Recommendations:

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

- Explore ways to sustain and utilize the infrastructure and capacity for CEM that were established during the COVID-19 pandemic, for example, the use of CEM to assess the safety of new and repurposed medicines in the future.
- Apply the lessons learned in managing funding, revision of study protocols, and lead time for approvals of future CEM projects in countries.

- Discuss these learnings during the next joint ACSoMP/GACVS meeting in November 2023, to optimize the implementation and use of CEM in pharmacovigilance.

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

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

A safety statement was published on WHO's website[3]. The link to the statement was added to the mhGAP website[4] and disseminated to relevant agencies, for example, to the UN Refugee Agency, United Nations Human Commissioner for Refugees (UNHCR). The next steps include a communication plan (e.g., press briefing) to ensure that the updated recommendations on valproic acid are disseminated to key stakeholders when the updated mhGAP guidelines are published in the second half of 2023. The key messages will be disseminated to non-governmental organizations (NGOs) and to national professional and patient organizations. The International Bureau for Epilepsy (IBE), an umbrella organization of national patient organizations is one NGO that is working closely with the Brain Health Unit of WHO for the dissemination of the mhGAP guidelines. The communication will include information about algorithms for alternative treatments and methods for medication switching. Local organizations will be involved in dissemination in low- and middle-income countries (LMICs) to ensure more effective and user-friendly communication. The guidelines will be tailored to reflect the availability of alternative treatments in countries. In addition, the mhGAP derivative products (intervention guide, training manuals, e-learning course, and mhGAP app) will be updated.

In the recent 2023 meeting of the Expert Committee on WHO Model Lists of Essential Medicines, there was an application for the inclusion of levetiracetam on the Essential Medicines List (EML) and Essential Medicines List for Children (EMLc), supported by the Brain Health Unit. The outcomes from the meeting with the updated Model Lists will be published late June, but the application, expert reviews, and public and WHO comments, which were all favourable, are available online[5]. It was recognized by both the EML team and the Brain Health Unit that, having alternative treatments available on the EML list is critical

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

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

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

to support the appropriate use of anti-seizure medicines by women of childbearing potential and by pregnant women.

Recommendations:

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

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

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

Recommendations:

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

Miltefosine and ocular events: update

A statement from ACSoMP on measures to minimize the risk of ocular adverse events associated with miltefosine was published on 12 April 2023[6]. The link to this statement was shared with various stakeholders. The first meeting of a WHO Guideline Development Group to develop the WHO clinical guidelines on leishmaniasis and to review the benefit-risk of

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

miltefosine in its different indications, based on the conclusions from a multidisciplinary technical group (MTG), was held in April 2023.

A draft patient information brochure has been developed to facilitate communication on the risk of ocular adverse events with miltefosine. This brochure will need local adaptation and user testing and can then be printed and distributed by the national leishmaniasis programme. This brochure is not intended to replace the patient information leaflet, which is a regulatory document. The communication strategy will ensure that the information reaches all the relevant target audiences. The next steps include preparing a public assessment report, and, based on the lessons learned, developing a standard operating procedure (SOP) on how WHO can facilitate the assessment of serious adverse events reported with products used in public health programmes, and their timely communication.

Recommendations:

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

Updates on malaria treatment during pregnancy

WHO has combined their guidelines for malaria treatment, vector control, etc. into one living document that is continually being updated as new evidence becomes available using WHO's transparent, rigorous guideline development process. The latest guidelines recommend that pregnant women with malaria should be treated in the first trimester with artemisinin-based combination therapies. The guidelines are available on the WHO website[7], and can also be accessed through the MAGICapp[8].

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

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

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

[8] WHO Guidelines for malaria. Geneva: World Health Organization (https://app.magicapp.org/#/guideline/7089, accessed June 2023).

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

Recommendations:

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