Report of the Meeting of the WHO Advisory Committee on Safety of Medicinal Products, 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.

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[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/pvg/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)

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.

Recommendation for active surveillance in future pandemics

- 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

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[4] Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders. Geneva: World Health Organization; 2023.

[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).

risk of impaired fertility males in the UK[6]. 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

[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).

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.