

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

14-16 June 2022

WHO convened the first joint meeting (virtual) of the **WHO Global Advisory Committee on Vaccine Safety (GACVS)** and the **WHO Advisory Committee on Safety of Medicinal Products (ACSOMP)** from 14 to 16 June 2022.

An integrated WHO Pharmacovigilance team was established in 2020, to combine work related to the safety of medicines and vaccines within the Department of Regulation and Prequalification (RPQ). Following this transformation, WHO convened a joint meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP) and the Global Advisory Committee on Vaccine Safety (GACVS) for the first time on 14–16 June 2022. A summary of the presentations and recommendations from the medicines-specific sessions and from the sessions of common interest for the pharmacovigilance of medicines and vaccines is provided below. The medicines-specific 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) 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 and Dr Gerald Dal Pan.

Survey on sodium valproate

Valproate containing products are known teratogens, and the risk of congenital malformations, developmental disorders are well documented. WHO has added a cautionary note on the use of valproate in pregnant women and women of childbearing potential in the Essential Medicines List (EML) and has amended the WHO mental health gap action programme (mhGAP) intervention guide to include warnings against the use of valproate in pregnant women and women of childbearing potential. Many high-income countries (HICs) have taken regulatory measures such as introducing pregnancy prevention programmes to minimize the risks, and the impact of these interventions are being assessed. However, there is very little information on the usage of valproate products or risk minimization measures in low- and middle-income countries (LMICs). To bridge this gap in knowledge WHO plans to design a survey to investigate valproate usage in LMICs. The WHO Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services, the Indian Pharmacopoeia Commission (IPC) and Pharmacovigilance Programme of India (PvPI), have already conducted a survey in India. This survey will be a starting point, from which the WHO survey will be designed. IPC were invited to present their experiences and lessons learned. The main objectives of the survey were to assess the impact of the awareness campaign on the teratogenic risks of valproate containing medicines and understand the knowledge, attitude and practices of healthcare providers towards the use of valproate containing medicines.

Recommendations:

Based on lessons learned, ACSoMP recommends that WHO consider the following when designing their survey:

- Consider including interviews as well as a survey to maximise responses and when analysing data, stratify by speciality of responders to understand potential confounders and biases.
- Information on alternative treatment should be collected to understand the context of valproate prescribing, additionally there is value in targeting questions to ask about potential obstacles to using alternatives (e.g., cost, access, awareness).
- It would be useful to follow-up children exposed during pregnancy, to assess any long-term effects, particularly in young males who have been exposed to valproate products. The use of pregnancy or disease-specific registries could be useful to assess the impact of sensitization following an awareness campaign over time.
- The Committee also recommended that paediatricians should be included in awareness campaigns since they can prescribe valproate-containing treatments and as children progress to adolescence and adulthood, they may already be taking the drug and be unaware of the risk should pregnancy occur.
- The Committee requested that the next ACSoMP meeting will include a session to review any updates from the Essential Medicines List (EML).

Update on eye disorders during leishmaniasis treatment with miltefosine

Miltefosine is an oral anti-infective that was authorized in India in 2002 for the treatment of some forms of leishmaniasis, including post-kala-azar dermal leishmaniasis (PKDL). PKDL presents as a skin rash that occurs

after successful treatment of visceral leishmaniasis that occurs in all *Leishmania donovani* endemic areas. Miltefosine was included in the Essential medicines list (EML) in 2011 and was authorized in USA and Germany in 2014. Since 2016, 60 cases of ocular disorders, including permanent blindness, following miltefosine treatment have been reported in India, although causality has not been established to date. In February 2022 WHO published a statement that included recommendations for health professionals, and this was actively shared globally with all WHO regions, with a particular focus on countries in the South-East Asia region, especially Bangladesh and Nepal where miltefosine has also been used. In April 2022, the South-East Asia Regional Technical Advisory Group on visceral leishmaniasis (kala-azar) shared ACSoMP's concerns, and they sought prompt responses from WHO and Member States. Further, WHO is setting up a multistakeholder expert group to advise WHO on the causal relationship, provide recommendations on the need to update risk minimization measures, and for further studies to address remaining uncertainties.

Recommendations:

- The Committee requested the opportunity to comment on the developed terms of reference (ToR) for the multistakeholder expert group.
- It was highlighted that all available evidence, including quality, non-clinical and clinical data should be considered, and it was recommended that safety data from other products from the same therapeutic class should also be explored. To facilitate future benefit-risk reviews, the number needed to harm and number needed to treat should be calculated.
- WHO should ensure adequate awareness of the current published recommendations in all countries where miltefosine is used. A standard operating procedure (SOPs) for pre-treatment ophthalmic examination and examinations every two weeks, once treatment with miltefosine is started, has been developed in India and this could be shared to facilitate implementation in other countries.
- A multi-country active pharmacovigilance study should be conducted to improve both data collection and awareness, building on existing disease programmes.
- ACSoMP expressed interest in a proposal from the WHO Country Office in India to lead a pharmacogenomic / molecular study in India to provide quick results, in accordance with recommendations made by the multidisciplinary group.

Safety of COVID-19 therapeutics updates

An update of the latest published recommendations for COVID-19 therapeutics and an outline of the process used to develop the recommendations by the WHO COVID-19 guideline development group were shared. WHO has published the 11th version of the 'Therapeutics and COVID-19' living guidance and the 4th version of the 'Clinical management of COVID-19' guidance.^{1,2} The assessment pipeline for COVID-19 therapeutics is updated weekly.³

The recommendations are graded as strong or conditional, based on the strength of the evidence and provide information on target population and populations who should not be treated, as well as specific conditions to be respected during treatment, including duration, and warning about potential drug-drug interactions. Guidance on information for patients and what, if any, safety monitoring should be done is provided. Derivatives, such as webinars, toolkits and treatment algorithms, based on the guidelines have been developed to disseminate the information.

Discussions/conclusions:

The general approach used, and the use of network meta-analyses for assessment of comparison treatments were discussed. Most studies that have been reviewed were performed in high income countries (HICs), although some have included patients in LMICs. While the relative risk from the studies may not differ with location the absolute risk may vary. This can affect the generalizability of the guidance. Generalizability is discussed in the guidance, and the locations of the studies are noted, but they are not taken into account in analyses.

Active surveillance: methods and data management tools

Molnupiravir, the first oral treatment for non-severe COVID-19 disease, received a WHO conditional recommendation for use on 3 March 2022. One of the conditions is that there should be a robust, active pharmacovigilance programme in countries using this product. To respond to this requirement, on 11 March 2022, WHO published a protocol for cohort event monitoring (CEM) studies on molnupiravir in LMICs. The plan for the implementation of the protocol in 6 to 12 countries was shared with the Committees. This plan consists

¹ World Health Organization. 2022. Therapeutics and COVID-19: living guideline. Available from: <https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.3>, accessed 17 June 2022.

² World Health Organization. 2021. Living guidance for clinical management of COVID-19. Available from: <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2>, accessed 2 July 2022.

³ World Health Organization. 2022. Therapeutics and COVID-19. Available from: <https://www.who.int/teams/health-care-readiness/covid-19/therapeutics>, accessed 22 July 2022.

of developing a training programme, and data collection, management and transfer tools. WHO has started developing the data collection and management tools, these will be useable in studies assessing other treatments and vaccines, even in clinical trials. Data will come from diverse sources, and at various times throughout the monitoring period. IT solutions are needed for both study participants and study-site staff as well as principal investigators. In addition, as the study will be carried out in numerous countries, the IT solutions need to be available in different languages and with flexibility to adapt to the local context.

Recommendations:

- The joint Committees recommended that case report forms (CRFs) should be adapted to pick up gestational age at time of exposure for the baby, when following pregnant women who were inadvertently exposed to the medicine, particularly since the exposure time is short.
- CRFs should be adapted to prompt participants to report concomitant over-the-counter medications.
- Different countries have different data privacy laws for collection and sharing of data. When a final list of countries that will implement the protocol is available, a strategy for respecting these laws should be developed.

Monitoring safety in pregnancy

WHO has three ongoing initiatives to improve safety monitoring during pregnancy. The first is a collaborative project between the Pharmacovigilance team and PATH (formerly known as the Program for Appropriate Technology in Health) aiming to map and assess the strengths and limitations of pregnancy exposure registries available in LMICs. The second is an internal WHO project, to map various WHO initiatives to assess the availability of minimal data elements to study pregnancy and neonatal outcomes in LMICs and to propose methods to harmonize these data elements. The third project is the monitoring of the safety of COVID-19 vaccines during pregnancy, which is a collaboration with the WHO Sexual and Reproductive Health and Research team.

An Expert Steering Committee (ESC), set up to oversee the first two projects, will provide independent, authoritative, and scientific advice to WHO on the safety of health interventions in pregnancy, and for the implementation of pregnancy exposure registries and other methods for monitoring the safety in pregnancy in LMICs. This will be critical for the preparation of LMICs for the safe introduction and use of health products in pregnant women. The ESC will also provide best practice guidance on the safety monitoring of health interventions in pregnancy.

The third initiative, the WHO COVID-19 pregnancy cohort study, is a longitudinal cohort study that comprises about 21 000 consecutively recruited pregnant women who will be followed every 4 to 6 weeks up to 6 weeks postpartum, to capture information on maternal, pregnancy, perinatal, neonatal and postpartum outcomes as well as non-pregnancy related outcomes. Information on COVID-19 vaccination status, when and which vaccine was administered will also be collected. Consistency between countries and study sites for outcome definitions, such as gestational age, and the data collected will be maximized by the use of standardized case report forms and standardized training provided to the investigators

As of June 2022, over 10 000 women have been recruited in eight countries, including about 4500 vaccinated women, of whom about 1700 and 1300 were exposed and unexposed, respectively, to SARS-CoV-2 infection. This study is very labour, time and resource intensive and the rapidly evolving pandemic adds to the challenges for running this type of study, but it is hoped that this initiative will help to strengthen the existing infrastructure for the future.

Discussions and conclusions:

The committee discussed collection of comorbidity data and controlling for confounding factors, sample size, consistency between countries and complexities around the determination of SARS-CoV-2 infections during pregnancy. The Committee encouraged the continuation of the cohorts and the use of the existing infrastructure after this study, so that important data on maternal and neonatal outcomes can continue to be collected.

Updates on the framework for WHO Listed Authorities

The framework and specifications for WHO listed authorities (WLAs) were developed in response to changes to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) structure in 2015 which had an impact on the definition of stringent regulatory authorities (SRAs). The definition of WLA, to be used to replace the concept of SRA, was adopted by the Expert Committee for Specifications for Pharmaceutical Products (ECSPP) in October 2020 (WHO TRS 1033), and corresponds to a regulatory authority or a regional regulatory system that has been documented to comply with all the relevant indicators and requirements specified by WHO for the requested scope of listing, based on an established benchmarking and a performance evaluation process. The objectives are to build capacity consistent with good regulatory practices in Member States as well as to promote regulatory cooperation, convergence and

transparency through networking, work sharing and reliance. In 2021 a policy document describing the purpose, definitions and high-level operating principles related to the evaluation and public listing of authorities was published.⁴

The WLA was launched on 31 March 2022.⁵ The voluntary process is initiated following a request from a Member State for a national or regional regulatory authority (RA) that must have a maturity level 3 to be eligible for performance evaluation. To be publicly listed as a WLA the RA will undergo a performance evaluation process, which differs from benchmarking processes as it is more like an inspection and audit and is not intended to help build capacity. The approach is based on the established global benchmarking tool (GBT) and a performance evaluation framework (PEF), which is a series of new indicators and tools for performance evaluation. The PEF has seven performance evaluation indicators (PEIs) which are assessed during a field trip. These are described in a specific manual that also has checklists. The PEF is being piloted in two to four countries. Based on these experiences the PEF manual will be updated and the WLA operational guidance will be published by the end of 2022.

Discussions and conclusions:

The promotion of reliance by the WLA initiative was discussed. The benefits of the WLA process and recognition of regulatory decisions made by WLAs to manufactures and procurement agencies were highlighted. Overall WLA will contribute to facilitating access to good quality medicinal products and vaccines.

⁴ World Health Organization. 2021. Evaluating and publicly designating regulatory authorities as WHO listed authorities Available from: <https://www.who.int/publications/i/item/9789240023444>. Accessed 21 June 2022.

⁵ World Health Organization. 2022. Interim manual for the performance evaluation of regulatory authorities seeking the designation as WHO listed authorities. Available from: <https://www.who.int/publications/m/item/a-framework-for-evaluating-and-publicly-designating-regulatory-authorities-as-who-listed-authorities-wla>. Accessed 21 June 2022.