WHO convened the second joint meeting (hybrid) of the World Health Organization (WHO) Global Advisory Committee on Vaccine Safety (GACVS) and the WHO Advisory Committee on Safety of Medicinal Products (ACSOMP) from 14 to 16 December 2022\(^1,2\).

Following the WHO transformation in 2020, in which the work related to the safety of medicines and vaccines were combined within the Regulation and Safety Unit (REG), joint meetings of the Advisory Committee on Safety of Medicinal Products (ACSoMP) and the Global Advisory Committee on Vaccine Safety (GACVS) were established. A summary of the presentations 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 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 (USFDA) 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.

**Update on molnupiravir active safety surveillance pilot study**
Molnupiravir was conditionally recommended in March 2022 for the treatment of mild to moderate COVID-19 infection in those at highest risk of hospitalisation. The conditional recommendation reflects the concern about its widespread use before more safety data become available, and mitigation strategies include undertaking active pharmacovigilance surveillance.\(^3\) To support the WHO clinical guidelines, WHO has published a protocol for a cohort event monitoring (CEM) study and is supporting countries to implement it. CEM is an active surveillance method that can be used to follow-up early users of molnupiravir to ensure timely collection of post-marketing safety data.\(^4\) The primary objective of the CEM study is to characterize and estimate the incidence of all adverse events (AEs) and serious AEs (SAEs). The secondary objectives included the characterization and estimation of the prevalence of maternal and perinatal outcomes in women inadvertently exposed to molnupiravir during pregnancy. The Pan American Health Organization (PAHO) has also adapted the protocol for use in their region. The progress of this study was presented to ACSoMP. Currently, WHO is supporting four countries to implement the study (Bangladesh, Egypt, Jordan and the Philippines). Countries are at the stage of obtaining country specific ethics approval and two countries are expecting to start data collection in the first quarter of 2023. WHO Headquarters (HQ) has developed a generic digital platform to collect data from multiple data sources with mobile and Internet tools and pool the data at a central hub at WHO. This tool will be useful.

---

\(^1\) https://cdn.who.int/media/docs/default-source/pvg/acsomp/acsomp-composition.pdf?sfvrsn=7c4030da_2


for data collection in other safety surveillance studies in the future. A statistical analysis plan has been developed and WHO will update the protocol to include the safety monitoring of nirmatrelvir-ritonavir, which is also a WHO recommended COVID-19 treatment.

Advice and conclusions

- ACSoMP recommended that WHO should promptly communicate the results from any interim analyses that become available to the ACSoMP Subcommittee for COVID-19 therapeutics.

Update on ocular adverse events during leishmaniasis treatment with miltefosine

Miltefosine is an oral anti-infective and one of the medicines with established efficacy in the treatment of some forms of leishmaniasis, a parasitic infection spread by sandflies. Leishmaniasis can take different forms, including cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL). Post-Kala-Azar Dermal Leishmaniasis (PKDL) is a sequela which generally occurs 6 months to several years after apparent cure of VL. It is generally prevalent in areas endemic for L. donovani in South Asia (Bangladesh, India and Nepal) and East Africa (mainly in Sudan). Although uncommon, leishmanial ocular infections have been reported, and keratitis and uveitis can also occur with the disease. A 12-week treatment course of miltefosine is used to treat PKDL in South Asia.

Following reports of ocular adverse events in patients treated with miltefosine, originating mostly from South-Asia, ACSoMP has previously recommended that WHO investigate this issue further. The proposed method was discussed with ACSoMP in June 2022 and WHO established a Multidisciplinary Technical Group (MTG) to advise on the causality, the risk characteristics and frequency, risk minimization measures, risk communication, remaining uncertainties and the need for further studies. To facilitate the work of the MTG, WHO, supported by the German National Regulatory Authority (BfArM) and the Uppsala Monitoring Centre (UMC), collected and compiled all available evidence and information on the causal relationship between reports of serious ocular events and exposure to miltefosine. The findings and recommendations from the MTG were presented to ACSoMP.

Based on the evidence, the MTG concluded that a causal relationship between ocular adverse events and the exposure to miltefosine is at least a reasonable possibility. The risk of ocular adverse events was observed mostly during the treatment of patients, both men and women, with PKDL in south Asia, including children under 18 years old, and were mostly observed beyond 28 days of treatment. No other risk factors were identified. Most, but not all, ocular events resolved after miltefosine was withdrawn or symptomatic treatment, e.g., steroids and topical antibiotics, was started.

Advice and conclusions

- ACSoMP supported the recommendations from the Multidisciplinary Technical Group (MTG), including:
  - the inclusion of the proposed warning and list of ocular adverse events in the summary of product characteristics and the patient information leaflet for miltefosine. All stakeholders should ensure that product information is provided in a language that is understood by local healthcare professionals and patients to enable effective risk communication;
  - the additional guiding principles for the prevention, early detection and management of eye complications in patients treated with miltefosine;
  - the development of a patient information brochure by WHO based on the MTG recommendations to facilitate risk communication;
communication via a statement on WHO’s website, the publication of the
corporal assessment report and publications in peer-reviewed journals
communication of conclusions through disease programmes and to
investigators of identified ongoing clinical trials;
in countries where it is feasible, a Direct Healthcare Professional
Communication by national regulatory authorities;
the use of active surveillance (such as a cohort event monitoring (CEM) study),
supported by a follow-up questionnaire, to characterize the risk and its
frequency and to assess the effectiveness of the risk minimization measure;
Collaboration of PV programme with disease programme, to ensure efficient
real time data sharing, rapid analysis and interpretation;
implement a study analysing miltefosine pharmacokinetics, the presence of
parasites and immune reactions in patients with PKDL to assess the specificity
and causality of this adverse event in these patients.

Update on hallucinations reported with Delamanid in children
Delamanid has been recommended for use in treating multidrug-resistant tuberculosis (MDR-
TB) or rifampicin resistant tuberculosis (RR-TB). The current WHO recommendation is that
delamanid may be included in the treatment of MDR/RR-TB patients of all ages, as part of a
longer regimen. (conditional recommendation. Moderate certainty of evidence for MDR/RR-
TB patients aged 3 years or more; very low certainty of evidence for children with MDR/RR-
TB aged below 3 years). In October 2021, ACSoMP discussed the signal of hallucinations in
children treated with Delamanid and recommended that the signal should be evaluated further
with a specialist in childhood psychology and sleep disorders. ACSoMP recommended that
the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring
Centre (UMC) in collaboration with other relevant experts should do an in-depth
investigation. The results of this investigation were presented by UMC to ACSoMP. They
showed that although the term ‘hallucinations’, particularly ‘hypnopompic hallucinations’
were given in the reports, the profiles of most cases seemed to be more consistent with
nightmares or night terrors, which mostly disappeared when treatment ended. It was
concluded that sleep disorders are common in children and difficult to distinguish from
adverse effects of medications. However, the association between sleep disorders (night
terrors and nightmares) and the use of delamanid indicates a possible relationship.

Advice and conclusions
- ACSoMP carefully assessed the response to this safety signal and feel that the
  response has been appropriate.
- Given that the product label has been modified by the market authorization holder to
  include hallucinations as an adverse event, and the potential of misclassifying ‘night
  terrors’ and ‘nightmares’, which are common in child development, as
  ‘hallucinations’, the risk mitigation actions already undertaken by the market
  authorization holder were considered to be sufficient and ACSoMP recommended that
  a ‘watch and wait’ strategy would be reasonable since the evidence of hallucinations
  in children is uncertain.

Update on dolutegravir exposure at conception and neural tube defects
Dolutegravir (DTG) has been regularly discussed by ACSoMP in recent years. DTG is a widely used and highly effective antiretroviral medication recommended for HIV/AIDS treatment. In 2018, confidence in this medicine was shaken when preliminary results from a nationwide birth surveillance programme in Botswana found a potential association between periconceptional exposure to DTG with the development of neural tube defects (NTDs) in a setting without a folate supplementation programme. However, as the cohort of this study grew in subsequent years, the prevalence of NTD in women with periconceptional exposure to DTG was no longer significantly higher than in women without periconceptional exposure to DTG or efavirenz or any other comparison group. This refutes the initial NTD signal, as the signal was based on a relatively small number of exposures, and has since been corrected with larger number of exposures. An update of the results from studies in other settings continue to show that DTG is highly effective and safe in pregnant women and that NTDs are not more frequent following periconceptional exposure. Although DTG has been shown to be an effective HIV treatment, the initial signal seems to continue to have an impact on women’s uptake in lower- and middle-income countries (LMICs) and a gap still exists between uptake by men and women.

**Advice and conclusions**

- ACSoMP considered that the results of the studies were reassuring and need to be communicated more widely and effectively, for example, by engaging with regulators in the regions to ensure effective integration of these results in patient information leaflets;
- ACSoMP recommended that communication strategies should include actions for patients and field healthcare professionals;
- ACSoMP recommended that the lessons learnt should be used to inform strategies to improve the use of medical products and vaccines in pregnant women more broadly;
- ACSoMP requested that information on DTG use and updated data on the safety of new, long-acting antiretrovirals for HIV prevention and treatment in pregnant women continue to be reported annually to them.

**Sodium valproate use in women and girls of childbearing potential: Update of WHO’s Mental Health Gap (mhGAP) guidelines**

The use of sodium valproate/valproic acid-containing products in women and girls of childbearing potential has been discussed in previous ACSoMP meetings. The Committee was informed of the upcoming Mental Health Gap (mhGAP) guideline update which has recommendations for the treatment of epilepsy and bipolar disorder in addition to other mental health conditions. The Guideline development group (GDG) reviewed evidence for the effectiveness and safety of antiseizure medicines in women and girls of childbearing potential and the recommendation for the use of valproic acid in this population will be updated. The updated mhGAP guideline is expected to be published this year. Meanwhile, WHO has published an addendum to the mhGAP Intervention Guide to reflect that valproate should not be used in women and girls of childbearing potential because of potential harm to the foetus ([https://cdn.who.int/media/docs/default-source/brain-health/mhgap_ig_v4_0(08032022).pdf?sfvrsn=696f27df_21](https://cdn.who.int/media/docs/default-source/brain-health/mhgap_ig_v4_0(08032022).pdf?sfvrsn=696f27df_21)).

ACSoMP discussed the importance of communicating the risks of valproic acid during pregnancy and emphasized the need to make resources and tools available to improve knowledge at the country-level. There is a need to raise awareness early in women’s reproductive life and to provide guidance on alternative treatments.
Advice and conclusion
ACSoMP recommended that a pre-guideline announcement, advocacy, communication and training materials should be developed urgently ahead of the publication of the revised guidelines;

- ACSoMP recommended that there is a need for communication about alternative treatments and medication switching methods;
- ACSoMP recommended that more effective and user-friendly methods for communicating this risk should be explored in LMICs.

Update on therapeutic guidelines for mpox and emergency use protocol for tecovirimat under the MEURI framework
On 23 July 2022, WHO declared the global mpox outbreak a public health emergency of international concern after reports of mpox outbreaks in several non-endemic countries. The mpox virus is a member of the Orthopoxvirus genus in the Poxviridae family and is related to the virus that caused smallpox, that was eradicated in 1980. Tecovirimat is an antiviral that inhibits p37, a highly conserved protein in all Orthopoxviruses. In January 2022, the European Medicines Agency authorized its use for smallpox, mpox, cowpox, and vaccinia complications in adults and children. The American CDC has a protocol for expanded access to allow access to and use of tecovirimat for treatment of non-variola Orthopoxvirus infections, including mpox, in adults and children. There are several ongoing randomized clinical trials but results will not be available until mid-2023, at the earliest. Although there is insufficient evidence to inform clinical management guidelines, WHO has developed the emergency use protocol under the MERUI (Monitored Emergency Use of Unregistered and Experimental Interventions) ethical framework to provide access to tecovirimat to patients with mpox and to characterize the clinical characteristic of the cohort receiving tecovirimat including the monitoring of any adverse or serious adverse events. WHO will convene an independent Data Monitoring Committee (DMC) to review the AEs and to report findings to national sponsors, relevant authorities and others DMCs. Serious AEs and suspected unexpected serious adverse reactions (SUSARs) will be reported via national pharmacovigilance systems to the WHO global database of individual case safety reports, VigiBase.

Update on ACSoMP Subcommittee activities on COVID-19 therapeutics
The ACSoMP COVID-19 Subcommittee was set up in January 2022 to review, evaluate and interpret post-introduction COVID-19 medicine safety data and to advise WHO on the overall safety of COVID-19 medicines and the need for additional monitoring or risk mitigation as well as the communication strategy of the safety data. The Subcommittee has held eight meetings since it was set up and has reviewed available postmarketing safety data for baricitinib, molnupiravir, nirveltramir-ritonavir sotrovimab, and tocilizumab.

Advice and conclusions
- ACSoMP recommended improving methods to detect safety signals in LMICs and that the safety of a wider variety of products, particularly those used in LMICs should be assessed.
Update on monitoring safety during pregnancy and breastfeeding projects: Pregnancy Exposure Registries Landscape Analysis (PERLA) and the COVID-19 pregnancy cohort study

Monitoring safety in pregnancy was discussed in the previous joint ACSoMP and GACVS meeting. An update on the progress of the Pregnancy Exposure Registries Landscape Analysis (PERLA) was provided. This project is a collaboration between the WHO Pharmacovigilance team and PATH (formerly known as the Programme for Appropriate Technology in Health). The project aims to identify registries, databases, surveys and other sources in LMICs that record exposure to drug and vaccine products during pregnancy and the subsequent maternal and perinatal outcomes. A literature search, a key informant survey and interviews were used to gather information. A report will be finalized in the first quarter of 2023 and results will be submitted for publication in the second or third quarter of 2023.

An update on the WHO COVID-19 pregnancy cohort study was also provided, this longitudinal study was developed early in the COVID-19 pandemic and captures information on maternal, pregnancy, perinatal, neonatal and postpartum outcomes in pregnant women. In the November 2022 updated protocol vaccine-related outcomes, data collection forms and analyses were added. The study is being conducted in eight countries in five WHO regions. Enrolment started in June 2021 and is expected to terminate in the second quarter of 2023. The enrolled women are followed every 4–6 weeks and up to 6 weeks postpartum and the neonates are followed for 4 weeks postpartum. The study will assess COVID-19 vaccine uptake during pregnancy, describe symptoms and non-pregnancy-related events after vaccination during pregnancy and if feasible, determine if the risk of adverse outcomes differs in pregnant women who received COVID-19 vaccine during pregnancy and those who did not.

As of 2 December 2022, 15,538 pregnant women and 8,143 vaccinated pregnant women had been enrolled. Over 60% of the vaccinated pregnant women have received non-mRNA vaccines. Some limitations to the study design include the difficulty of studying rare outcomes and signals, although data can be pooled across countries to increase the statistical power to detect rarer events. In addition, the study is labour-, time- and resource-intensive. The infrastructure that has been established will be available for future studies of other exposures of pregnant women.

Advice and conclusions

- ACSoMP and GACVS suggested that it would be very useful to maintain the infrastructure of the study to enable maternal and neonatal data to be collect routinely, although they recognized there could be challenges, such as resources.

Serious games approach to risk and safety communication strategies: ‘The Good Talk!’

The serious games approach was discussed as a potential risk communication strategy for pharmacovigilance. Serious games are designed to be interactive, fun and entertaining (motivating) while they educate, train or change users’ (i.e., players’) behaviour, while addressing issues such as vaccine hesitancy and misunderstanding of adverse events and

---

mistrust. ‘The Good Talk!’ is an application based on the serious games approach to increase the skills of vaccine advocates to enable them to have open conversations about COVID-19 vaccination with their close contacts who are vaccine hesitant. Once the game has been finalized, a low-bandwidth deployment package will be available that can be adapted to local contexts by changing the graphics, the text and names, while the underlying method remains the same. An evaluation protocol to determine how effective the tool is in terms of changing people’s behaviour in each new setting will be included in the deployment package.

Declaration of interests; All members of Advisory committees are requested to fill in a declaration of interest form prior to each meeting. All experts were cleared in having no conflicts declared, or when declared, assessed as nonconflicting.

Funding sources: This publication is possible thanks to the generous contributions to WHO from our Member States and other donors.