Recommendations of the 18th meeting of the WHO Advisory Committee on the Safety of Medical Products

26–28 October 2021

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) was established in 2003 to provide advice to WHO on safety issues relating to medicinal products. The 18th meeting of ACSoMP was held virtually on 26–28 October 2021 and was co-chaired by Dr June Raine of the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom and Dr Gerald Dal Pan of the United States Food and Drug Administration (USFDA).

A summary of the conclusions and recommendations from the 18th meeting of ACSoMP is provided below.

An integrated approach to pharmacovigilance and vaccine safety monitoring

Reorganization in WHO led to the formation of a Medicines and Health Products (MHP) Division with two departments – one on Health Product Policy and Standards (HPS) and one on Regulation and Prequalification (RPQ). During the transformation, former medicines and vaccines safety teams merged into one team dealing with pharmacovigilance and the safety of medicinal products in the RPQ department. The Committee noted that the combined focus would facilitate future work on the safety of medicines and vaccines globally and this new arrangement in WHO reflected the systems in operation in many countries.

Dolutegravir and data review of neural tube defects, September 30, 2021

Dolutegravir (DTG) has been regularly discussed by members of ACSoMP in recent years. DTG is a widely used and highly effective antiretroviral medication recommended for treatment of people with HIV/AIDS, but the confidence in this medicine was shaken in 2018, when preliminary results from a nationwide birth surveillance programme in Botswana found a potential association between periconceptional DTG exposure with the development of neural tube defects (NTDS) in a setting without folate fortification. However, as the cohort expanded over subsequent years, there was a significant decline in the strength of the signal, with the prevalence of NTDs with preconception exposure to DTG no longer being significantly different than observed with non-DTG preconception antiretroviral treatment exposures. Studies in other settings have supported these subsequent findings. Although the results of the Tspamo study is showing a very positive balance of benefit to risk of a very effective medicine, there is a concern that some countries remain hesitant to use DTG despite its effectiveness.
Recommendations: ACSoMP recommends that this misconception is corrected because it limits regimen harmonization across populations, and, in turn, impedes DTG-based ART scale up efforts. Models such as Tspamo study are recommended to be used in future to study all medicines and vaccines given during pregnancy. Pregnancy exposure registries and birth defect

surveillance systems in LMIC settings would support the assessment of therapeutic and preventive interventions on maternal and birth outcomes.

Sodium valproate and pregnancy

The WHO Expert Committee on the Selection and Use of Essential Medicines at its 23rd meeting in June–July 2021 added a cautionary note with the listings of sodium valproate to indicate that its use should be avoided in pregnant women and women of childbearing potential. Current WHO guidelines include recommendations for use of valproate in patients with epilepsy and bipolar disorder. However, because the use of valproate in women of childbearing age during the preconception phase leads to a high risk of birth defects and developmental disorders in infants, WHO's recommendations on valproate for epilepsy and bipolar disorders in pregnant or breast-feeding women state that: 1) women with epilepsy should have seizures controlled as well as possible with the minimum dose of antiepileptic drug taken in monotherapy, wherever possible, and that valproate should be avoided in women of childbearing age; and that 2) in women, with bipolar mania planning a pregnancy or, in women who are pregnant or breastfeeding, valproate should be avoided due to risk of birth defects. It was noted that newer medicines need to be made more available in LMICs and that WHO is reviewing the current evidence for valproate and other medications in women of childbearing age and is updating the recommendations for their use in epilepsy and bipolar disorders.

Recommendations: Concerns about the continued inappropriate and dangerous use of valproate in women of childbearing age should be advocated as it is known that this drug causes a certain proportion of children to be born with malformations every year. Although educational material has increased awareness of these dangers amongst healthcare professionals in some settings, sodium valproate is still being prescribed. More work is needed to understand why practices do not coincide with increased awareness. Monitoring safety of medicines during pregnancy should be revisited in future ACSoMP meetings.

Monitoring the safety of medicines used in leprosy

WHO's leprosy team requested advice from ACSoMP on the monitoring of leprosy medicines, most of which are old and have known adverse effects. There is basically little data on adverse drug reactions collected through reporting systems with leprosy medicines.

Recommendations include:

- Developing a pharmacovigilance package containing a watch list of adverse reactions of concern together with advice on their management and prevention to help minimize risk, as many of the medicines used in leprosy are older drugs with a known safety profile. The package should also contain advice on studies to be carried out. Further investigations into the effectiveness of thalidomide for treatment of erythema nodosum

leprosum reactions in leprosy and follow up cohort studies to monitor harms and quantify risks were suggested.

- National leprosy programmes could usefully learn from the experience of tuberculosis programmes with regard to active surveillance and IT solutions for data sharing.
- The upcoming consultation by the WHO leprosy programme in November 2021 should focus on the development of a future programme of work that would include a range of pharmacovigilance priorities that would form the basis of global activities and help build stakeholder ownership of the leprosy programme and its work.

Tuberculosis signal on hallucinations with delamanid in children

Delamanid has been recommended for use in treating multidrug-resistant tuberculosis (MDR-TB) or rifampicin-resistant tuberculosis (RR- TB). In May-June 2021 WHO convened a Guideline Development Group (GDG) meeting on the management of TB in children and adolescents. Among the data reviewed was information from the manufacturer (Otsuka Pharmaceuticals) on a safety signal of hallucinations. WHO recommended that delamanid may be used as part of longer regimens in children with MDR-/RR-TB aged below 3 years. Children of all ages treated with delamanid need to be closely monitored throughout the duration of treatment. The signal of hallucinations was discussed during the ACSoMP meeting.
Recommendations: The signal of hallucinations should be evaluated further and a specialist in childhood psychology and sleep disorders should be requested to consider the evidence. An in-depth investigation of this signal should be facilitated by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre in collaboration with other relevant experts. Additionally, reporting of adverse events with delamanid directly to VigiBase should be encouraged.

Visceral leishmaniasis: ocular adverse events with miltefosine

The advice of ACSoMP was requested for managing the signal of eye disorders during the treatment of leishmaniasis with miltefosine. Miltefosine is the first and only oral antileishmanial medicine and is listed in WHO's Essential Medicines List (EML). Depending upon the parasite species and endemic areas of its presence, miltefosine is one of the medicines indicated (either as monotherapy or combined with other leishmaniasis medicines) for all four clinical forms of leishmaniasis, i.e. cutaneous, mucocutaneous, visceral (VL) and post-kala-azar dermal leishmaniasis. In South-East Asia miltefosine has been used in VL patients for 28 days per oral daily treatment and currently for 12 weeks per oral daily treatment for PKDL.

In India, between 2004-2014, more than 200,000 VL patients have been treated with miltefosine and during the period 2016 and 2020, some 6322 post-kala-azar dermal

leishmaniasis (PKDL) patients were treated. Of these, since 2019, 48 patients (age range 8–72 years) have reported an ocular adverse event following the use of miltefosine.

Recommendations:

- Risk management regarding the use of miltefosine is needed. At the same time, there is a need for further information. Early communication, detection and management of ocular events is extremely important since early withdrawal could reduce the problem. A statement from WHO to raise awareness should be issued as soon as possible.
- Eye examinations are essential in order to find out exactly what is causing the problem and there is a need to study the safety of miltefosine beyond 28 days therapy.
- Laboratory tests should be conducted to investigate potential impurities, and quantities of the drug in each capsule.
- A multistakeholder subgroup of ACSoMP on miltefosine will be established to get a clearer understanding of this issue.
- Pharmacovigilance for Kala-azar elimination programme should be strengthened.

African trypanosomiasis – update on fexinidazole in DRC

Human African Trypanosomiasis (HAT), or sleeping sickness is lethal without treatment, tends to be found in poor rural areas, often on the borders of countries and remote from urban centres. Fexinidazole was obtained a positive scientific opinion through Article 58 by the EMA for treatment of HAT, after considering the benefits and risks of the medicine in November 2018. As one of the conditions for the positive approval, EMA asked Sanofi to conduct a phase 3 post-authorization safety study of fexinidazole.

An update on a planned post-authorization safety study of fexinidazole in the treatment of HAT was presented during the ACSoMP meeting. So far, there have been reports on 126 patients receiving fexinidazole, – far fewer than expected – partly due to the fact that the disease is becoming rarer and also because there are long delays in receiving data. Eighty eight of the 126 patients experienced some kind of adverse event. Two patients died – one most likely from an unrelated cause and one from suicide. The same drug was evaluated in South America for Chagas disease and several cases of depression were reported, including one case of suicide. Suicidal ideation has now been added to the formal description (SmPC) of fexinidazole. The issue of suicidal ideation is important since several medicines are known to be associated with this.

Recommendations: A suggestion for proactive data collection in this particular context was made. ACSoMP acknowledged the progress made so far and recommended that the safety data from the EMA is made available to the Advisory Committee in future.