MINUTES OF THE 4TH MEETING OF THE PHARMACOVIGILANCE RISK ASSESSMENT EXPERT COMMITTEE

The National Pharmacovigilance Centre, Division of Pharmacy Services, Drug Regulatory Authority of Pakistan
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DRUG REGULATORY AUTHORITY OF PAKISTAN
Telecom Foundation Complex, 7th Mauve Area, G-9/4, Islamabad

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Minutes of the 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee.

The 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held in the Committee Room of the Drug Regulatory Authority of Pakistan (DRAP) on the 26th of February, 2024. The meeting started with the recitation of the Holy Quran and salutation upon the Holy Prophet (P.B.U.H).

The meeting was attended by the following members:

S. No	Name	Designation
1	Brig. ® Dr Akbar Waheed, Professor of Pharmacology, Islamic International College, Rawalpindi.	Chairman
2	Dr. Obaidullah, Director, Division of Pharmacy Services, DRAP.	Co-Chair
3	Mr Abdul Mateen, Deputy Director, Division of Pharmacy Services, DRAP	Secretary
4	Prof. Dr Madeeha Malik, Professor, Pharmacy Practice, Hamdard Institute of Pharmaceutical Sciences, Islamabad.	Member
5	Dr Maryyum Sarfraz, Associate Professor, Health Services Academy, Islamabad. attended virtualy	Member
6	Mr Muhammad Taimoor Chaudhary, Section Supervisor (Drug Chemistry Unit), Punjab Forensic Science Agency, Lahore.	Member
7	Syed Shamim Raza, Director Services Line and Chief Pharmacy Services, Agha Khan University Hospital, Karachi.	Member
8	Dr Khalid Mehmood, Associate Prof./Head of Pharmacy, Department of Pharmacy, Abbottabad University of Science & Technology, Abbottabad.	Member
9	Sardar Shabbir Ahmed, Senior Drug Inspector, Focal Person Pharmacovigilance Islamabad	Co-opted member

Mr Abdul Mateen, Deputy Director / Secretary presented the agenda.

1. MISCELLANEOUS ITEMS.

1.1. Confirmation of minutes of the 3rd meeting of PRAEC.

i. The 3rd meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held on the 8th of September, 2023. The draft minutes of the meeting were prepared and shared with expert members through email and were finalised in light of the emails of members on 20th September 2023.

ii. Accordingly, as per decisions of the 3rd meeting of PRAEC, the safety alerts were issued and decisions were also communicated to the concerned Divisions of the DRAP. However, safety alerts related to COVID-19 vaccines have not been communicated yet.

iii. The minutes of the 3rd meeting were placed before the PRAEC for confirmation as per the Standard Operating Procedure vide document no PHSR/SOP/PC/018.

Decision: All the members confirmed the minutes of the 3rd meeting of PRAEC held on the 8th of September, 2023.

1.2. Strengthening of Pharmacovigilance System in Public Health Programmes.

i. The Drug Regulatory Authority of Pakistan notified the Pharmacovigilance Rules, 2022 in April 2022. However, so far only Punjab and Islamabad have established their pharmacovigilance centres as well a centre of Federal Directorate of Immunization (FDI). The World Health Organization (WHO) in its recent visit also developed institutional development plans (IDPs) related to the establishment of vibrant pharmacovigilance centres and notification of pharmacovigilance committees in each province, territory and state as well as public health programmes at the Federal and provincial level. The Pharmacovigilance Risk Assessment Expert Committee (PRAEC) in its 3rd meeting held on the 8th of September, 2024 decided inter alia, that "*National Pharmacovigilance Centre, Pharmacy Services Division, DRAP will coordinate with vertical programmes at the national level for the establishment of pharmacovigilance centres in these entities including the constitution of pharmacovigilance committees/expert review safety panel etc*".

ii. In this regard, the NPC coordinated with the Directorate of Malaria Control and an MOU has already been signed for strengthening pharmacovigilance. Similarly, coordination with the T. B Control programme is in the process. To expedite the process of strengthening the pharmacovigilance systems, the NPC invited all the public health programmes to the 4th Meeting of PRAEC to apprise the members about the update and develop a future roadmap in light of WHO-IDPs.

iii. The following representatives from the Public Health Programmes attended the meeting:

   a. Dr Zafar Iqbal, Director (Technical), Federal Directoate of Immunization (FDI), Minsitery of National Health Services, Regulation and Coordination.

b. Dr Basharatullah Baig, Deputy Director, Monitoring and Evaluation, Federal Directorate of Immunization (FDI), Ministry of National Health Services, Regulation and Coordination.

c. Dr. Mukhtar, Director, Directorate of Malaria Control, Ministry of National Health Services, Regulation and Coordination.

d. Mr Sabir Qureshi, Manager Supply Chain, Common Management Unit, Ministry of National Health Services, Regulation and Coordination.

e. Mian Rehan Ahmed, Scientific Officer, Directorate of Malaria Control, Ministry of National Health Services, Regulation and Coordination.

Discussion:

A. Updates from the National Pharmacovigilance Centre:

Dr. Obaidullah, Director of the Division of Pharmacy Services and Head of the National Pharmacovigilance Centre (NPC), provided an insightful overview of pharmacovigilance activities in Pakistan. Key points of his presentation included:

a. The evolution of Pakistan's pharmacovigilance system spanning from 1994 to 2023. He elucidated the roles and responsibilities of national, provincial, and regional pharmacovigilance centres including public health programmes, in accordance with the Pharmacovigilance Rules, 2022. Additionally, he outlined institutional development plans (IDPs) based on identified tasks by the World Health Organization (WHO) during recent benchmarking exercises.

b. These plans aim to enhance Pakistan's pharmacovigilance framework and include the notification of the Pharmacovigilance (PV) system within Public Health Programs and Committees, the reinforcement of human resources across all levels, and the adoption of a uniform Adverse Drug Reactions (ADRs) collection system, specifically VigiFlow, within public health programs, hospitals, and treatment sites. To streamline pharmacovigilance reporting, the Uppsala Monitoring Centre has accedded to NPC's request for unlimited dedicated VigiFlow logins for healthcare professionals involved in public health programs and hospitals. This decentralization of VigiFlow aims to alleviate data entry burdens on provincial and national centres, allowing them to focus on other vital activities such as signal detection, management etc.

c. The launch of the National Pharmacovigilance Centre, DRAP's quarterly Pharmacovigilance Newsletter, which has already published two issues. The objectives of this newsletter encompass educating stakeholders on medication safety and encouraging the spontaneous reporting of ADRs in Pakistan. Additionally, the newsletter provides valuable insights into the detection, assessment, understanding, and prevention of adverse effects associated with medications.

d. The National Pharmacovigilance Centre, Division of Pharmacy Services, convened a meeting to strengthen the Pharmacovigilance System which was chaired by CEO-DRAP. The CEO emphasised DRAP’s commitment to achieving World Listed Authority Level III status, stressing the necessity of fortifying the pharmacovigilance system at every level in accordance with Pharmacovigilance Rules, 2022. The CEO-

DRAP also highlighted recent developments, including the launch of electronic submission for applications, and DRAP's commitment to achieving PIC membership. Furthermore, the efforts of the National Pharmacovigilance Centre with respect of the development of the pharmacovigilance programme of Pakistan including the publication of a Newsletter were also appreciated. He underscored the crucial role of coach audits in implementing new regulatory standards aligned with international practices. The following representatives from esteemed organizations including the Global Fund-UNDP, USP PQM+, Common Management Unit and Directorate of Malaria Control attended the meeting:

a. Mr. Soso Gesadze, Specialist Health Product Management, Global Fund,
b. Heather Doyle, Project Coordinator; HIV grant, Global Fund, UNDP.
c. Osama Musa Bella Hussain, Procurement Officer, HIV grant, Global Fund, UNDP;
d. Mr. Sardar Shabbir Ahmed, Focal Person Pharmacovigilance, Islamabad,
e. Mr. Muhammad Mukhtiyar, Director at Directorate of Malaria Control; and
f. Mr Waqas Ahmed, Chief of Party USP-PQM +;

g. The National Pharmacovigilance Centre highlighted collaboration opportunities with UNDP, the Global Fund, CMU, the Directorate of Malaria Control, and Regional Centres to enhance pharmacovigilance across all levels. Mr. Soso Gesadze, Specialist Health Product Management, Global Fund stressed the regulatory function's priority and urged active coordination between UNDP and DRAP for a robust system. Training and capacity building for pharmacovigilance personnel were emphasized. Heather Doyle, Project Coordinator and Osama Musa Bella Hussain, Procurement Officer, HIV Grand Global Fund-UNDP expressed commitment to supporting DRAP, especially in the pharmacovigilance domain, proposing its inclusion in ongoing Malaria and HIV grants within six months.

h. Furthermore, DRAP has successfully signed a Memorandum of Understanding (MoU) with the Directorate of Malaria Control to bolster the pharmacovigilance system in malaria control efforts. The agenda for today's meeting includes discussions on adopting a similar approach for other public health programs to expedite the implementation of pharmacovigilance rules and fulfil WHO-identified tasks.

B. Updates from Directorate of Malaria Control.

Dr Muhmmad Mukhtar, Director of the Directorate of Malaria Control, informed the committee that an MoU has been successfully executed with the Drug Regulatory Authority of Pakistan (DRAP) to enhance the pharmacovigilance system within the malaria control program and facilitate access to VigiFlow. He added that in the forthcoming week, the Directorate of Malaria Control (DoMC) will provide nominations for individuals to receive VigiFlow logins and commence data entry procedures accordingly. Additionally, it was conveyed that DoMC will establish a Pharmacovigilance Committee at the national level in alignment with DRAP's directives.

C. Updates from Federal Directorate of Immunization.

Dr. Zafar Iqbal, Director (Technical) and Dr. Basharatullah Baig, Deputy Director of Monitoring and Evaluation at the Federal Directorate of Immunization (FDI), shared status of AEFI reporting / collection and further processing alongwith other pharmacovigilance activities within the program. They highlighted that the COVID-19 pandemic paved the way forward for both the Drug Regulatory Authority of Pakistan (DRAP) and FDI, as it facilitated their integration in terms of pharmacovigilance efforts. The FDI had already established a functional National Adverse Events Following Immunization (AEFI) review committee, which became even more active during the pandemic. AEFI data collected through the National Immunization Management System Database (NIMS) were systematically entered into the VigiFlow database and subsequently shared with the Uppsala Monitoring Centre (UMC). The FDI has also updated its guidelines to incorporate VigiFlow reporting. However, post-pandemic, due to a shortage of human resources, the data entry process has not been meeting the requirements of the National Pharmacovigilance Centre (NPC). It was pledged that the FDI would reactivate the AEFI review committee and revise relevant procedures and guidelines in accordance with DRAP directives. Additionally, it was announced that VigiFlow would be fully adopted for AEFIs collected through routine immunization programs.

D. Updates from Common Management Unit

Mr. Sabir Qureshi, Supply Chain Manager, conveyed that the Common Management Unit (CMU) is dedicated to establishing a functional pharmacovigilance system within the public health programs under its purview. He mentioned that the Tuberculosis Control Program possesses adequate human resources to meet the pharmacovigilance requirements. Therefore, he suggested that VigiFlow logins may initially be distributed to PMDT sites across Pakistan. Emphasizing the significance of active surveillance for new drugs in public health programs, he stated that CMU will collaborate with DRAP to develop an effective pharmacovigilance system. Mr. Qureshi also disclosed that CMU will assist in forming pharmacovigilance committees either centrally or within each public health program. Furthermore, he mentioned that CMU will be granted access to the VigiFlow database to oversee the activities of public health programs.

Decision: PRAEC after detailed deliberation decided as follows:

a. **The National Pharmacovigilance Centre (NPC) will steer the activity of the pharmacovigilance programme of Pakistan and will provide guidance for the establishment of Pharmacovigilance centres in Public Health Programmes and will coordinate for adopting uniform VigiFlow database for ADR collection at all levels, alongside signing MOUs.**
b. **The Federal Directorate of Immunization will prioritize reactivating the AEFI review committee, implementing VigiFlow for routine immunization, and aligning procedures and guidelines in line with the National Pharmacovigilance Centre of DRAP.**
c. **The Directorate of Malaria Control will coordinate with DRAP to nominate individuals for VigiFlow database logins, establish its PV Committee, initiate data collection and reporting, and revise guidelines and procedures in accordance with DRAP standards / Pharmacovigilance Rules, 2022.**

d. **The Common Management Unit will facilitate the establishment of an effective pharmacovigilance systems within each program, including forming PV committees, launching active surveillance systems for new drugs, and coordinating with relevant entities for effective implementation.**

e. **Training of DRAP, regional centres and public health programms by international partners.**

f. **Updated status will be shared with PRAEC after 6 months.**

2. RELIANCE ON INTERNATIONAL SAFETY DECISIONS.

2.1. Levetiracetam and Clobazam: Rare and Serious DRESS reaction.

i. Levetiracetam is an antiseizure medicine indicated for use alone or together with other medicines to control certain types of seizures in adults and children such as partial seizures, myoclonic seizures, or tonic-clonic seizures. Clobazam is a benzodiazepine indicated for use in combination with other medicines to control seizures in adults and children 2 years and older who have a specific severe form of epilepsy called Lennox-Gastaut syndrome.

ii. The U.S. Food and Drug Administration (FDA) in November, 2023 warned that the antiseizure medicines levetiracetam and clobazam can cause a rare but serious reaction that can be life-threatening if not diagnosed and treated quickly. This reaction is called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) which may start as a rash but can quickly progress, resulting in injury to internal organs, the need for hospitalization, and even death. This hypersensitivity reaction to these medicines is serious but rare. DRESS can include fever, rash, swollen lymph nodes, or injury to organs including the liver, kidneys, lungs, heart, or pancreas. The FDA accordingly decided to add new warnings about DRESS to the prescribing information and the medication guide of levetiracetam and clobazam for patients and caregivers. It was informed that the warnings for both levetiracetam and clobazam medicines will include information that "early symptoms of DRESS such as fever or swollen lymph nodes can be present even when a rash cannot be seen. This is different from other serious skin-related reactions that can happen with these medicines and where a rash is present early on, including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN)."

iii. Healthcare professionals were informed that levetiracetam and clobazam have been linked to a rare, potentially life-threatening reaction called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), occurring 2-8 weeks post-treatment. This may lead to severe inflammation and organ damage, requiring prompt medical attention. Prescribers should inform patients, explain DRESS signs, and advise seeking immediate care. DRESS involves cutaneous reactions, eosinophilia, fever, and systemic complications. Early recognition, discontinuation, and supportive care are crucial. Patents were informed that levetiracetam and clobazam, prescribed for seizures, can trigger a rare but severe reaction called Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). This immune system response may cause widespread inflammation and organ damage, leading to hospitalization or death if untreated. Patients were advised not to stop medication abruptly and; to consult their healthcare professionals. DRESS symptoms, such as fever, rash, and

organ-related issues, may occur 2 to 8 weeks after starting treatment. Seek immediate medical attention for concerning symptoms.

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders should include information about rare and serious DRESS reactions in warning and precaution sections of the prescribing information/label of medicines containing levetiracetam and clobazam.**

b. **As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all registered medicines containing levetiracetam and clobazam in light of the decisions of US-FDA and PRAEC-DRAP.**

2.2. Topiramate: Risk of neurodevelopmental disorders in children during pregnancy.

i. Topiramate is a medicine used to treat epilepsy in adults and children aged two years and older. It is also indicated in adults for the prevention of migraines. At present, topiramate must not be used to prevent migraine or manage body weight during pregnancy and patients who can become pregnant must use effective birth control when using topiramate.

ii. The Medsafe of Newzealand in April, 2023 has announced that the product information for topiramate (Topamax®) is updated to include the risk of neurodevelopmental disorders and birth defects in children whose mothers were taking topiramate during pregnancy. The risk of neurodevelopmental disorders was noted in an observational study based on data from five Nordic (Denmark, Finland, Iceland, Norway, and Sweden) pregnancy registries. The registries captured information from over 24,000 children exposed to at least one antiepileptic medicine before birth. Of these children, 471 were exposed to topiramate alone. The authors reported a 2.77-fold increase in the risk of autism spectrum disorder and a 3.47-fold increase in the risk of intellectual disability in children with an epileptic mother taking topiramate during pregnancy compared to those with epileptic mothers not taking any antiepileptic treatment during pregnancy. Healthcare professionals were advised that topiramate should only be used to treat epilepsy in pregnancy if the potential benefit justifies the potential risk to the mother and fetus. Pregnancy testing should be performed before starting treatment, and women of childbearing potential should use a highly effective contraceptive method during treatment. The use of topiramate for migraine prophylaxis is contraindicated in pregnancy. Inform women of childbearing potential about the risks of fetal harm if they become pregnant and refer epileptic women taking topiramate who become or plan to become pregnant for specialist advice.

iii. The TGA, Australia in its product information safety update of June, 2023 has also announced that the product information for topiramate (Topamax®) is updated to include the risk of foetal neurodevelopment disorder, updated warning about women of childbearing potential, and contraindications in pregnancy and women of childbearing potential for migraine prophylaxis.

iv. The European Medicine Agency (EMA) in July, 2023 started a review to assess new data on a potential risk of neurodevelopmental disorders in children who have been exposed to topiramate during pregnancy. At that time, a study based on data from a Nordic registry that investigated the risk of neurodevelopmental disorders associated with several anti-epileptic drugs, including topiramate was published. The study conclusions suggested a possible increase in the risk of autism spectrum disorders, intellectual disability and child neurodevelopmental disorders with the exposure to topiramate during pregnancy. The PRAC decided at that time that further assessment was warranted to determine the scope and the best regulatory procedure to assess these potential risks.

v. Accordingly, the Pharmacovigilance Risk Assessment Committee (PRAC) (EMA's safety committee) in September, 2023 introduced further restrictions i.e. pregnancy prevention programme on the use of topiramate to be put in place. At present, topiramate must not be used to prevent migraine or manage body weight during pregnancy and patients who can become pregnant must use effective birth control when using topiramate. For patients using topiramate for the treatment of epilepsy, the PRAC is now recommending that the medicine should not be used during pregnancy unless there is no other suitable treatment available. The PRAC also recommends additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb. These measures will inform any woman or girl who is able to have children about the risks of taking topiramate during pregnancy and the need to avoid becoming pregnant while taking topiramate. The product information for topiramate-containing medicines will be updated to further highlight the risks and the measures to be taken. A visible warning will also be added to the outer packaging of the medicine. Patients and healthcare professionals will be provided with educational materials regarding the risks of using topiramate during pregnancy, and a patient card will be provided to the patient with each medicine package. The PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralized Procedures for Human (CMDH), which on 11 October 2023 endorsed new measures recommended by EMA's safety committee (PRAC). The CMDh has also agreed to additional measures, in the form of a pregnancy prevention programme, to avoid exposure of children to topiramate in the womb.

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, that registration holders should update the prescribing information of Topiramate to include the risk of foetal neurodevelopment disorder and warning about women of childbearing potential, and also include information about not using the Topiramate in pregnancy for the treatment of epilepsy unless there is no other suitable treatment available.**

b. **As per Rule 10 (1) (h) (ii) of Pharmacovigilance Rules, 2022, that registration holders should update contraindications in pregnancy and women of childbearing potential for migraine prophylaxis.**

c. As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all

registered medicines containing Topiramate in light of the decisions of MedSafe Newzealand, TGA-Australia, EMA-Europe and PRAEC-DRAP.

2.3. Miltefosine: Measures to minimise the risk of ocular adverse events.

i. 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 the bite of infected female phlebotomine sandflies. Leishmaniasis can take different clinical forms, including cutaneous leishmaniasis, mucocutaneous leishmaniasis, and visceral leishmaniasis (VL).

ii. The World Health Organization (WHO) through its medical product alert dated 12th April 2023 informed healthcare professionals and regulatory authorities of the risk of ocular adverse events in people who have taken miltefosine and provided advice on measures to minimize this risk in patients exposed to miltefosine.

iii. Following reports of ocular disorders following miltefosine use originating mostly from South Asia, the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) recommended WHO to further investigate this issue. The proposed method was discussed in June 2022 and WHO established an ad-hoc 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. The MTG was also supported by the WHO, the German National Regulatory Authority (BfArM) and the Uppsala Monitoring Centre (UMC).

iv. Based on the available data, the MTG considered that a causal relationship between ocular adverse events and exposure to miltefosine is at least a reasonable possibility. The risk of ocular adverse events, such as redness of the eye, inflammation of different eye structures (keratitis, scleritis, uveitis) and visual impairment up to blindness has been observed mostly during the treatment of patients with Post-Kala-Azar Dermal Leishmaniasis (PKDL) in South Asia in both men and women, including in children under 18-year-old, and mostly beyond 28 days of treatment. No further risk factors could be identified. When the information was available, most of the cases were resolved after miltefosine was withdrawn, sometimes after a symptomatic treatment was started. However, in some cases, the adverse ocular event led to permanent loss of sight. The frequency of adverse ocular events during treatment with miltefosine could not be estimated based on the available data, and the mechanism of action remains unclear.

v. Previously, the ACSoMP discussed during its meeting on 14th of December 2022 the issue of ocular adverse events with miltefosine and i*nter-alia* advised 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 along with the issuance of Direct Healthcare Professional Communication by National regulatory authorities.

vi. The following was advised to healthcare professionals:

- Before starting the miltefosine treatment the history of eye disorders should be collected and an eye examination should be done as appropriate.
- In case of current or past history of ocular disorder, the benefits and the risks of treating a patient with miltefosine should be carefully considered, and advice from an ophthalmologist should be sought where feasible.
- All patients should be informed before starting the treatment that in case of eye problems during the treatment (e.g. red eyes, increased watering, eye pain, blurred vision) they should discontinue miltefosine and contact their healthcare professional immediately.
- If ocular complications occur and a connection with miltefosine cannot be excluded, miltefosine should be discontinued immediately and an alternative treatment for leishmaniasis should be initiated if necessary. Since miltefosine has a very long half-life (>6 days), it is possible that ocular changes will not be reversible without treatment even after discontinuation of miltefosine. Therefore, an eye specialist should be consulted in such cases to avoid the possibility of permanent damage.

vii. Post-Kala-Azar Dermal Leishmaniasis (PKDL) is a sequela which can generally occur 6 months to several years after the apparent cure of VL. Although uncommon, leishmanial ocular manifestations 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 specific to VL endemic countries in Southeast Asia.

Decision: The PRAEC decided as follows:-

a. As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, that registration holders should update the prescribing information/ label of Miltefosine-containing medicines by including information in the warning and precaution section about the risk of ocular adverse events and also list these in adverse drug reaction section.

b. As per Rule 10 (1) (b) of Pharmacovigilance Rules, 2022 recommended the National Pharmacovigilance Centre to issue a safety alert/advisory related to the risk of ocular adverse events with Miltefosine-containing medicines.

c. As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all medicines containing Miltefosine in light of the decisions of WHO and PRAEC-DRAP.

2.4. Statins: Potential risks of myasthenia gravis and ocular myasthenia

i. Statins are HMG-CoA reductase inhibitors and include atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin. Statins are an acceptably safe and effective group of medicines that help lower the level of low-density lipoprotein (LDL) cholesterol in the blood. Statins play an important role in the treatment of atherosclerotic cardiovascular disease.

ii. The Pharmacovigilance Risk Assessment Committee (PRAC) of EMA in February, 2023 has recommended a change to the product information for statins to include potential risks of myasthenia gravis and ocular myasthenia. In a few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. Treatment with statins should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

iii. The MHRA-UK in September 2023 informed the healthcare professional and patient about the European's review recommendation related to new warnings on the risk of new-onset or aggravation of pre-existing myasthenia gravis with multiple statins. The findings of the European review were considered by the Pharmacovigilance Expert Advisory Committee (PEAG) of the Commission on Human Medicines (CHM), which agreed with the recommendations. It was informed that the product information of all statins is being updated to list myasthenia gravis and ocular myasthenia gravis as adverse drug reactions with a frequency 'not known'. New warnings will also be added to the Summaries of Product Characteristics and Patient Information Leaflets.

iv. Healthcare professionals were advised to refer patients presenting with suspected new-onset myasthenia gravis after starting statin therapy to a neurology specialist – it could be necessary to discontinue statin treatment depending on the assessment of the individual benefits and risks. Likewise, healthcare professionals should advise patients with pre-existing myasthenia gravis to be alert to the aggravation of symptoms while taking a statin; it could be necessary to discontinue statin treatment depending on the assessment of the individual benefits and risks.

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, that registration holders of statins (HMG-CoA reductase inhibitors) should update the warning and precaution section about the risk of myasthenia gravis and ocular myasthenia gravis and list as adverse drug reactions with a frequency 'not known' in the adverse drug reaction section.**

b. **As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all registered statins (HMG-CoA reductase inhibitors) in light of the decisions of MHRA-UK, EMA- Europe and PRAEC-DRAP.**

2.5. Mercaptopurine: Potential risk of hypoglycaemia

i. Mercaptopurine is indicated for the maintenance therapy for a specific type of cancer of the blood and bone marrow (acute lymphoblastic, lymphocytic leukaemia) in combination with other medicines in adults and children.

ii. Health Canada in May, 2023 announced that the product safety information for mercaptopurine is to be updated to include the potential risk of hypoglycaemia (low blood sugar) in children less than 18 years of age. This safety review was triggered by a U.S. Food and Drug Administration update to the product safety information for mercaptopurine-containing products to include the risk of hypoglycemia in children, as well as Canadian and international cases reported to the Canada Vigilance Program.

iii. Health Canada reviewed information provided by the manufacturer, and from the Canada Vigilance and published literature. Health Canada reviewed 23 cases (one domestic, 22 international), of which 22 cases were reported in children under 18 years of age and 12 cases were in children under six years of age. Of the 23 cases, six were found to be probably linked to the use of mercaptopurine, 15 (one domestic) were found to be possibly linked and two were unlikely to be linked. Health Canada also reviewed 8 articles published in the scientific literature, which showed a possible link between the use of mercaptopurine and the risk of hypoglycemia in children. In some of the studies, there was an increased number of cases seen in children under 6 years of age.

iv. Health Canada's review concluded that there may be a link between the use of mercaptopurine and the risk of hypoglycemia in children (less than 18 years of age). A large proportion of the reported cases were in children under 6 years of age. It was informed that Health Canada is working with the manufacturers of mercaptopurine-containing products to update the Canadian Product Monographs to include the risk of hypoglycemia in children.

Decision: The PRAEC advised the National Pharmacovigilance Centre to coordinate with 3 leading haematologists/oncologists for their opinion on the matter regarding the update of the warning and precaution sections of the prescribing information/ label of Mercaptopurine by including the risk of hypoglycemia in children less than 18 years, and to resubmit the case to PRAEC in its next meeting.

2.6. Sulfamethoxazole, trimethoprim: Risk of haemophagocytic lymphohistiocytosis (HLH)

i. The combination of sulfamethoxazole and trimethoprim is a prescription antibiotic medicine indicated for the treatment of various bacterial infections, such as urinary tract infections, respiratory tract infections, and gastrointestinal infections.

ii. Health Canada in May, 2023 announced that the product safety information for combination sulfamethoxazole and trimethoprim-containing products will be updated to include the risk of haemophagocytic lymphohistiocytosis (HLH). Triggered by a labelling update for these products by the EMA, Health Canada reviewed the available information from the Canadian and international databases, and the scientific literature. Of the ten cases

assessed, one case was found to be probably linked to the use of the medicine, eight were found to be possibly linked (including one fatal case) and one (another fatal case) was unlikely to be linked. The review found a possible link between the use of the medicine and the risk of HLH. HLH is a life-threatening syndrome of pathologic immune activation characterized by clinical signs and symptoms of extreme systemic inflammation (e.g. fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis) and is associated with high mortality rates if not recognized early and treated. Healthcare professionals were advised to immediately evaluate patients who develop early manifestations of pathologic immune activation. If HLH is diagnosed, discontinue sulfamethoxazole-trimethoprim treatment.

iii. Previously, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency in its meeting from 03-06 May 2021 considered the available evidence in EudraVigilance, the literature, and the data submitted by Roche/ Eumedica, Aspen Pharma and Teva regarding the risk of Haemophagocytic lymphohistiocytosis (HLH) with sulfamethoxazole/trimethoprim in combination and agreed that the available information is considered sufficient to support a warning statement in the product information of the drug combination.

Decision: The PRAEC decided as follows:-

d. As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 to update the warning and precaution section of the prescribing information/ label of the drug combination of sulfamethoxazole and trimethoprim by including information about the risk of haemophagocytic lymphohistiocytosis (HLH).

a. As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of the registered drug combination of sulfamethoxazole and trimethoprim in light of the decisions of EMA, Health Canada and PRAEC-DRAP.

2.7. Pseudoephedrine-containing medicines: Risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) and measures to minimize these risks.

i. Pseudoephedrine is a stimulant that is often used as a decongestant in people who have a cold or allergies.

ii. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) in its meeting held on 27-30th November 2023 recommended new measures for medicines containing pseudoephedrine to minimize the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) and informed that product information for all pseudoephedrine-containing medicines will be updated to include the risks. The recommendations follow a

review of all available evidence, including post-marketing safety data, which concluded that pseudoephedrine is associated with risks of PRES and RCVS. During the review, PRAC sought advice from an expert group of general practitioners, otorhinolaryngologists (specialists in diseases of the ear, nose, throat, head and neck), allergologists (specialists in the treatment of allergies) and a patient representative. PRAC also considered information submitted by a third party representing healthcare professionals. It was recommended that medicines containing pseudoephedrine are not to be used in patients with high blood pressure that is severe or uncontrolled (not being treated or resistant to treatment), or with severe acute (sudden) or chronic (long-term) kidney disease or failure. In addition, as part of its advice on safety-related aspects to other EMA committees, the PRAC discussed a direct healthcare professional communication (DHPC) with important information on pseudoephedrine-containing products which was also forwarded to EMA's human medicines committee (CHMP).

iii. RES and RCVS are rare conditions that can involve reduced blood supply to the brain, potentially causing serious, life-threatening complications. With prompt diagnosis and treatment, symptoms of PRES and RCVS usually resolve. Healthcare professionals should advise patients to stop using these medicines immediately and seek treatment if they develop symptoms of PRES or RCVS, such as severe headache with a sudden onset, feeling sick, vomiting, confusion, seizures and visual disturbances.

iv. On 25 January 2024, EMA's Committee for Medicinal Products for Human Use (CHMP) endorsed the measures recommended by the PRAC to minimise the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) for medicines containing pseudoephedrine. CHMP confirmed that medicines containing pseudoephedrine are not to be used in patients with high blood pressure that is severe or uncontrolled (not being treated or resistant to treatment) or in patients with severe acute (sudden) or chronic (long-term) kidney disease or failure. The CHMP opinion will now be sent to the European Commission, which will issue a legally binding decision across the EU.

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of the Pharmacovigilance Rules, 2022 that registration holders should update the warning and precaution section of the prescribing information/label of pseudoephedrine-containing medicines by including information about the risks of posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome (RCVS) along with advise that medicines containing pseudoephedrine are not to be used in patients with high blood pressure that is severe or uncontrolled (not being treated or resistant to treatment), or with severe acute (sudden) or chronic (long-term) kidney disease or failure.**

b. As per Rules 10 (1) (h) (vi) registration holders should issue direct healthcare professionals communication by highlighting the risk.

c. As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of registered Pseudoephedrine-containing medicines in light of the decisions of EMA and PRAEC-DRAP.

2.8. Valproic Acid (sodium valproate): Risks associated with the use in women and girls of childbearing potential and potential risks in male patients.

i. Valproate (as sodium valproate or valproic acid) is authorised for use in epilepsy and bipolar disorder.

ii. The World Health Organization (WHO) in a safety statement dated 2nd of May 2023 alerted stakeholders to the revised guidance on the use of valproic acid (sodium valproate) for the treatment of epilepsy and bipolar disorder in women and girls of childbearing potential. It was informed that valproic acid (sodium valproate) should not be prescribed to **women and girls of childbearing potential** because of the high risk of birth defects and developmental disorders in children exposed to valproic acid (sodium valproate) in the womb. In women and girls of childbearing potential, lamotrigine or levetiracetam should be offered as first-line monotherapy for both generalized onset seizures and focal onset seizures.

iii. **For women and girls of childbearing potential who are currently prescribed valproic acid** (sodium valproate), the WHO also stated that advice should be provided on the use of effective contraception, without interruption, during the entire duration of treatment. Information must be provided on risks associated with valproic acid (sodium valproate) use during pregnancy, pregnancy prevention and referral for contraceptive advice if they are not using effective contraception. Individual circumstances should be evaluated in each case when choosing the contraception method and involving the woman in shared decision-making. If a woman is planning to become pregnant, a person trained in the management of epilepsy/bipolar disorder in pregnant women should consider alternative treatment options. Women should be informed to consult their physician as soon as they are planning pregnancy and the need to urgently consult their physician in case of pregnancy. Every effort should be made to switch to appropriate alternative treatment before conception. If switching is not possible, the woman should receive further counselling regarding the risks of valproic acid (sodium valproate) for the unborn child to support her informed decision-making. A specialist should periodically review whether valproic acid (sodium valproate) is the most suitable treatment for the person.

iv. The EMA's safety committee (PRAC) in its meeting held on 8-11 January, 2023 recommended precautionary measures for the treatment of male patients with valproate medicines. These measures are to address a potential increased risk of neurodevelopmental

disorders in children born to men treated with valproate during the three months before conception. In reaching its conclusion, the PRAC reviewed data from a retrospective observational study carried out by companies that market valproate as an obligation following a previous review of valproate use during pregnancy. The committee also considered data from other sources, including non-clinical (laboratory) studies and scientific literature, and consulted patients and clinical experts. The PRAC's latest recommendations come in addition to restrictions and other measures that are already in place to avoid valproate exposure in pregnancy, because exposed babies are at high risk of malformations and developmental problems. These measures were endorsed following a referral of valproate and related substances in 2018. The measures at that time included a ban on the use of such medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available.

v. PRAC also discussed a direct healthcare professional communication (DHPC) for valproate medicines which will be forwarded to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh). When adopted, the DHPC will be disseminated to healthcare professionals by the marketing authorization holders. The DHPC will inform healthcare professionals about the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months prior to conception. It is recommended that valproate treatment in male patients is started and supervised by a specialist in the management of epilepsy, bipolar disorder or migraine. Valproate treatment of male patients should be reviewed regularly to consider whether it remains the most suitable treatment, particularly when the patient is planning to conceive a child.

vi. On 22nd January, 2024, the United Kingdom, medicine and Health Product Regulatory Agency (MHRA) through a drug safety update informed that new safety and educational materials had been introduced for men, women and healthcare professionals to reduce the harm from valproate, including the significant risk of serious harm to the baby if taken during pregnancy and the risk of impaired fertility in males. Healthcare professionals were advised to review the new measures and materials and integrate them into their clinical practice when referring patients and when prescribing or dispensing valproate. Healthcare professionals were advised that valproate must not be started in new patients (male or female) younger than 55 years unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available. At their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate, however subsequent annual reviews will only require one specialist general practice and pharmacy teams should continue to prescribe and dispense valproate and if required offer patients a referral to a specialist to discuss their treatment options.

vii. Valproate has a high teratogenic potential. Exposure to valproate in pregnancy is associated with physical birth defects in 11% of babies and neurodevelopmental disorders in up to 30-40% of children, which may lead to permanent disability. Since 2018, valproate has been

contraindicated in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme (PPP) are followed. The purpose of PPP was to ensure all women and girls are fully informed of the risks and the need to avoid exposure to valproate medicines in pregnancy through an annual review and signing a risk acknowledgement form.

viii. In 2022, the Commission on Human Medicines (CHM) reviewed the latest data on the safety of valproate. The CHM heard from patients and other representatives about how valproate was being used and how the risks were currently managed. The CHM noted that data from the Medicine and Pregnancy Registry showed that pregnancies in England continue to be exposed to valproate. The CHM also considered other known risks of valproate, including the risk of impaired male fertility. The CHM considered pre-clinical data on possible transgenerational risks with prenatal exposure, as well as data from studies in juvenile and adult animals suggesting adverse effects on the testes. There are currently limited data available on many of these risks in humans and further studies are planned. However, the CHM noted many patients receiving valproate have other therapeutic options with fewer potential reproductive harms.

ix. On 28th November 2023, MHRA issued a National Patient Safety Alert to instruct Integrated Care Boards (in England), Health Boards (in Scotland), Health Boards (in Wales), and Health and Social Care Trusts (in Northern Ireland) to prepare for the new risk minimisation measures by 31 January 2024. The new safety and educational materials support these measures. Due to the known significant risk of serious harm to a baby after exposure to valproate in pregnancy, these measures aim to ensure valproate is only used if other treatments are ineffective or not tolerated, and that any use of valproate in women of childbearing potential who cannot be treated with other medicines is in accordance with the Pregnancy Prevention Programme (PPP).

x. The CHM will consider further recent registry data which may suggest an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception. In the study, around 5 children in 100 born to fathers treated with valproate around conception were diagnosed with a neurodevelopmental disorder. This is compared to 3 in 100 children whose fathers were taking lamotrigine or levetiracetam around conception (two other anti-seizure medicines). As a precaution, male patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options. Moreover, MedSafe, Newzealand on 7th December 2023 informed that the data sheet and the consumer medicines information leaflet of sodium valproate (Epilim) have been recently updated with additional information use in people who can father children.

Decision: The PRAEC decided as follows:-

a. As per Rule 10 (1) (h) (ii) of the Pharmacovigilance Rules, 2022 that registration holders of sodium valproate should update the contraindication not to prescribe sodium valproate-containing medicines in following situations:

i. **In pregnancy, if there is no other effective or tolerated treatment available and individual benefit-risk assessment is performed and documented for each patient; and**

ii. **In women of childbearing potential aged under 55 years, unless there is no other effective or tolerated treatment available, followed by individual benefit-risk assessment and the patients are made aware of pregnancy prevention programme.**

b. **As per Rule 10 (1) (h) (vi) of the Pharmacovigilance Rules, 2022 that registration holders should initiate an awareness Programme for Pregnancy Prevention (PPP) for sodium valproate-containing medicines.**

c. **As per Rule 10 (1) (h) (iv) of the Pharmacovigilance Rules, 2022 that registration holders should also update the warning and precaution section of the prescribing information/ label of sodium valproate-containing medicines by including information about high-risk of birth defects and neuro-developmental disorders in children exposed to valproic acid (sodium valproate) in the womb and about the minor potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the three months before conception and as a precaution advise male patients on valproate who are planning a family within the next year should speak to a healthcare professional about their treatment options.**

d. **As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information/ label of sodium valproate-containing medicines in light of the decisions of WHO, EMA, MHRA-UK and PRAEC-DRAP.**

2.9. Tranexamic acid injection: Risk of medication errors resulting in inadvertent intrathecal injection.

i. Tranexamic acid (TXA) is a lifesaving medicine; however, this potential clinical risk should be considered and addressed by all operating theatre staff. Reviewing of existing operating theatres' drug handling practices are required in order to decrease this risk, such as storage of TXA away from the anaesthetic drug trolley, preferably outside the theatre.

ii. WHO in its medical product alert on 16th March 2022 alerted healthcare professionals about the risk of administration errors that can potentially occur with tranexamic acid (TXA) injection. There have been reports of TXA being mistaken for obstetric spinal anaesthesia used for caesarean deliveries resulting in inadvertent intrathecal administration.

iii. In TXA administered intrathecally, potent neurotoxin and neurological sequelae are manifested, with refractory seizures and 50% mortality. The profound toxicity of TXA administered intrathecally was described in 1980. A 2019 review identified 21 reported

cases of inadvertent intrathecal injection of TXA since 1988, of which 20 were life-threatening and 10 fatal. Sixteen were reported between 2009 and 2018.

iv. WHO recommends early use of intravenous TXA within 3 hours of birth in addition to standard care for women with clinically diagnosed postpartum haemorrhage (PPH) following vaginal births or caesarean section. TXA should be administered at a fixed dose of 1g in 10 ml (100 mg/ml) IV at 1 ml per minute, with a second dose of 1g IV if bleeding continues after 30 minutes.

v. TXA is frequently stored in close proximity with other medicines, including injectable local anaesthetics indicated for spinal analgesia (e.g., for caesarean section). The presentation of some of the local anaesthetics is similar to the TXA presentation (transparent ampoule containing transparent solution), which can erroneously be administered instead of the intended intrathecal anaesthetic resulting in serious undesirable adverse effects. Recently, obstetricians from several countries have reported inadvertent intrathecal TXA administration and related serious neurological injuries.

Decision: The PRAEC decided as per Rule 10 (1) (b) and 10 (1)(h) (vi) of Pharmacovigilance Rules, 2022 and recommended National Pharmacovigilance Centre to issue safety alerts/ advisory related to the risk of medication errors due to inadvertent intrathecal Tranexamic acid injection.

2.10. Propofol: Medication errors that could potentially lead to life-threatening/fatal cases

i. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA in April 2023 recommended that Market Authorization Holders for propofol-containing products should submit a variation to amend the product information of the outer and immediate packaging to include "For single use in one patient. Risk of sepsis in multiple use" and "Use immediately after opening". In case of insufficient space on the immediate packaging, the National Competent Authorities may decide to omit parts of the warning on the immediate packaging. The PRAC has considered the available evidence in EudraVigilance, literature and the responses of the MAHs for this decision

Decision: The PRAEC decided as per Rule 10 (1) (h) (iv) and as per Rule 10 (1)(e) to recommend to the Registration Board to direct registration holders of propofol-containing medicine to introduce outer or immediate packaging information of "For single use in one patient. Risk of sepsis in multiple use" and "Use immediately after opening" on the outer carton of propofol injection to avoid medication errors as per Rules.

3. ADDITIONAL AGENDA.

3.1. Implementation status of the decisions taken by PRAEC in its previous meeting.

Members emphasized during the meeting the necessity of implementing decisions made by the Pharmacovigilance Risk Assessment Committee (PRAEC) to uphold patient safety. It was underscored that registration holders and relevant forums within the Drug Regulatory Authority of Pakistan (DRAP) need to put coordinated efforts to update label/prescribing information and execute any regulatory or risk minimization measures initiated by PRAEC. Additionally, enhancing communication between the National Pharmacovigilance Centre and relevant implementing forums (both inside and outside DRAP) was deemed essential.

Decision: The committee advised that the National Pharmacovigilance Centre should obtain information regarding the implementation status of earlier decisions made by PRAEC. This data should be submitted to PRAEC for review and consideration in the upcoming meeting

3.2. Direct reporting of pharmacovigilance data by hospitals to the National Centre.

Syed Shamim Raza, Chief Pharmacy Services, Agha Khan University Hospital, Karachi / Member of PRAEC highlighted the existence of pharmacovigilance data collection systems in both public and private sector hospitals across provinces, indicating their potential contribution to Pakistan's pharmacovigilance program. However, the absence of provincial pharmacovigilance centres impedes data reporting from these hospitals. PRAEC stressed the importance of stakeholders fully adhering to Pharmacovigilance rules and urged the implementation of decisions made in the 3rd meeting regarding establishing provincial centres and forming pharmacovigilance committees. They suggested that if establishing provincial centres proves difficult, the National Pharmacovigilance Centre should devise an alternative system or directly collaborate with hospitals to provide database logins for direct reporting. Many hospitals are willing to report data, but the lack of provincial centres obstructs this process.

Decision: It was decided that the National Pharmacovigilance Centre (NPC) has online means such as Medvigilance E-Reporting and MedSafety Mobile application where healthcare professionals and hospitals could report directly. However, concerning the provision of database logins to the hospitals, it was decided that NPC would initially coordinate with provincial health departments to expedite the establishment of their centres. If it takes much time, then NPC should allocate Vigiflow logins to such hospitals.

The meeting ended with vote of thanks to and from the Chair.