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.