MINUTES OF THE 5TH 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
Prime Minister's National Health Complex, Park Road, Islamabad.

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Minutes of the 5th meeting of the Pharmacovigilance Risk Assessment Expert Committee.

The 5th 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 2nd of January, 2025. 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	Abdullah Diyo, 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	Mr. Shoukat Sahad, Chief Pharmacist, Rehman Medical Institute (RMI), Peshawar.	Member
6	Mr Muhammad Taimoor Chaudhary, Section Supervisor (Drug Chemistry Unit), Punjab Forensic Science Agency, Lahore. (Attended via Zoom)	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 (Pharmacovigilance-I)/Secretary presented the agenda.

1. Miscellaneous Items.

1.1. Confirmation of minutes of the 4th meeting of PRAEC.

i. The 4th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held on the 26th of February, 2024. The draft minutes of the meeting were prepared and shared with expert members for any comments and were finalised on the 11th of March, 2024. The meeting was chaired by Brig. (R) Dr. Akbar Waheed, Professor, Islamic International College, Rawalpindi.

ii. Accordingly, as per decisions of the 4th meeting of PRAEC, the safety alerts were issued and decisions were also communicated to the concerned Divisions of the DRAP and necessary coordination with public health programmes was carried out.

iii. The minutes of the 4th meeting were accordingly placed before the PRAEC in its 5th meeting held on the 2nd of January, 2025 for confirmation as per the Standard Operating Procedure (SOP) vide document No PHSR/SOP/PC/018.

Decision: All the members confirmed the minutes of the 4th meeting of PRAEC held on the 26th of February, 2024.

1.2. Strengthening of Pharmacovigilance System in the country.

i. The Drug Regulatory Authority of Pakistan notified the Pharmacovigilance Rules, 2022 in April 2022. The World Health Organization (WHO) formally benchmarked the Regulatory System of Pakistan for World Listed Authority level 3 status, in May 2023, wherein proposed various institutional development plans (IDPs) related to the establishment of vibrant pharmacovigilance centres and notification of pharmacovigilance committees in each province, territory and state.

ii. In this regard, Provincial Focal Persons of Pharmacovigilance were invited to the 3rd meeting of PRAEC held on the 8th of September, 2024 wherein, the following was decided:

   a. Provincial, territorial, and state health departments should nominate focal persons (if pending) and notify pharmacovigilance centres, committees, and officers as per Pharmacovigilance Rules, 2022 at the earliest.

   b. A uniform ADR tool, VigiFlow, will be piloted by Provincial Pharmacovigilance Centres, granting access to 3-5 officers from major hospitals. The DRAP will provide necessary logins and training on data entry.

   c. c. DRAP and health departments will enhance pharmacovigilance units by increasing staff and infrastructure at all levels.

   d. Awareness efforts will promote ADR reporting in public and private healthcare facilities.

iii. Thereafter, the WHO conducted a 1st review meeting for the proposed IDPs in March 2024 and recommended timely implementation of proposed IDPs. The DRAP started

active coordination with provinces and established Pharmacovigilance Centre in AJK and Khyber Pakhtunkhwa along with already two provincial centres of Punjab and Islamabad. Furthermore, 29 hospitals from these 4 provinces were integrated into the VigiFlow database and necessary training was provided. Meanwhile, the DRAP also conducted a two-day workshop on the implementation of WHO recommendations for strengthening the National Regulatory System at Lahore, where the Pharmacovigilance Focal persons and representatives from provinces were invited. At the end of the meeting, the following road map was agreed upon for the implementation of Institutional Development Plans (IDPs) for Cross-Cutting Regulatory Functions to Strengthen the National Regulatory System of Pakistan.

iv. The WHO also conducted its 2nd review meeting in November 2024 and expressed its concern about the non-establishment of Pharmacovigilance Centres, notification of committees in all provinces and harmonisation of procedures and tools. Below is the status of the pharmacovigilance system in Pakistan as of 31st of December, 2024.

Provincial Centre Established	a. The Punjab b. Islamabad c. Khyer Pakhtunkhwa d. Azad Jammu and Kashmir	
Statistic **Total ADRs in 51,967 VigiFlow of Pakistan**	Pharma Companies	17,977
	E-Reporting/ Mobile App/E-Forms	401
	Federal Directorate of Immunization	32,186
	The Punjab	732
	Islamabad	670
	Khyer Pakhtunkhwa	1
	Azad Jammu and Kashmir	0
Provincial Pharmacovigilance Committee	Only in Punjab. None in other provinces.	
Number of Hospitals from Provinces integrated into VigiFlow	The Punjab	**7**
	Islamabad	4
	Khyer Pakhtunkhwa	11
	Azad Jammu and Kashmir	10

v. Provincial Pharmacovigilance Focal Persons were invited to the 5th meeting of PRAEC to update the committee about the recent development in light of the roadmap for earlier implementation of Pharmacovigilance Rules, 2022 and achievement of level 3 status of WLA in respect of pharmacovigilance function.

vi. The following Focal Persons from Provincial Pharmacovigilance Centres and Provincial Health Departments attended the 5th meeting of PRAEC-DRAP:

S. No	Name	Designaion
1	Mr. Sardar Shabbir Ahmed	Secretary, PQCB, Focal Person PV, Islamabad.
2	Ms Nusrat Rehman.	Director, Pharmacovigilance, Directorate of Drugs Control, Punjab, Lahore.
3	Ms Fouzia Ashraf	State Focal Person & Secretary QCB Azad Jammu & Kashmir, Muzaffarabad.

4	Mr. Ubaid Khan	Focal Person Pharmacovigilance and Chief Drug Inspector, Gilgit Baltistan
5	Dr Inam Ul Haq Fazal Haq	Assistant Director, Pharmacy Services, Focal Person, PV. Directorate of Drugs Control and Pharmacy Services, Khyber Pakhtunkhwa, Peshawar
6	Mr. Muhammad Salik Zahid	Chief Drug Inspector, Baluchistan, Quetta.
7	Mr. Abdul Razzak Memon	Deputy Director, Directorate of Pharmacy Sindh.

Discussion:

Intially, Abdul Mateen, Deputy Director (PV-I) and Focal Person, Pharmacovigilance, National Pharmacovigilance Centre, DRAP gave a presentation about the status of pharmacovigilance activities in the country. He informed about the different meetings held and communication made with provinces for the establishment of provincial pharmacovigilance centres, notification of the pharmacovigilance committees, and nomination of pharmacovigilance officers from hospitals from the VigiFlow logins.

Brig. ® Dr Akbar Waheed, Chairman, PRAEC emphasised that awareness and sensitization of hospitals at the Tehsil and periphery level is also required. People and the hospital's administration are unaware of pharmacovigilance which is why extensive awareness targeted against each stakeholder is required through newsletters, press releases, and medical college journals. Awareness in Newspapers was also suggested.

Mr Sardar Shabbir Ahmed informed that the Pharmacovigilance Committee of Islamabad has been finalised and is submitted to the Government for approval as per Pharmacovigialnce Rules, 2022. Further, the Islamabad Pharmacovigilance Centre (IPC) is also strengthening its human resources and in this regard, positions for dedicated Pharmacovigilance officers (POs) have been advertised. It was pledged that ADRs reporting from hospitals of Islamabad to whom logins have been provided will be increased through active follow-up and coordination. Sensitization at a higher level is the need of the hours as only nomination of POs would not suffice the requirement.

The need for an enhanced reporting culture in the country was emphasised by Syed Shamim Raza from Agha University Hospital, who advised that direct access to private hospitals should be provided if Provincial Pharmacovigilance Centres are not yet established in some provinces. Other members also advised adding private hospitals to the VigiFlow database as these hospitals have a system in place for the collection, reporting and assessment of reports. Reporting culture should be enhanced by promoting ADR reporting as a non-punitive activity. It was briefed that the Pharmacovigilance Officers have not only the responsibility to report ADR but also to take complete measures for awareness and reporting as per Pharmacovigilance Rules, 2022. The National Pharmacovigilance Centre-DRAP should coordinate with all private sector hospitals in

respect of VigiFlow logins, the appointment of sufficient Pharmacovigilance Officers at least 1/200 beds of hospitals and the constitution of pharmacovigilance committees.

Ms Nusrat Rehman from Punjab Pharmacovigilance Centre (PPV) informed that Punjab has notified Pharmacovigialnce Officers at the level of Tehsil Headquarters Hospitals as per Pharmacovigilance Rules, 2022. However, due to a busy schedule, reporting is low as Pharmacovigilance Officers are assigned other duties by the hospital's administration. There is a need for awareness and coordination from DRAP or any other higher forum with the administration of the hospitals so that pharmacovigilance officers can focus on ADR reporting.

Ms Fouzia Ashraf, there is a shortage of Human Resources for Pharmacovigilance in Azad Jammu and Kashmir. The Pharmacovigilance committee has been discussed with higherup and will be notified in due time. Coordination among healthcare professionals and pharmacists is missing that why there is low reporting. Mr Ubaid Khan informed that the Provincial Focal person and Pharmacovigilance Officers from the hospital have been nominated by the Health Department of Gilgit Baltistan and the committee will shortly notified. The assignment of pharmacovigilance officers as an additional charge and the lack of dedicated officers are some of the reasons for the lack of a functional pharmacovigilance system in provinces.

Dr Inam Ul Haq informed that the summary for the notification Pharmacovigilance Centre of Khyber Pakhtunkhwa is pending on the cabinet agenda. It was informed that the focal persons for the VigiFlow have been nominated from public hospitals; however, now officers from private hospitals will be nominated. With regard to low ADRs reporting from the province, it was informed that an extensive training session has been planned where focal persons will be trained. Active coordination from the DRAP level was suggested to enhance reporting. Mr Abdul Razzak Memon informed that the nomination of the Provincial Focal Person and from hospitals has been finalised and submitted to the Health Department of Sindh for notification. Mr. Muhammad Salik Zahid committed to expediting the nomination of Focal Persons from Balochistan.

Decision: PRAEC after detailed deliberation decided as follows:

a. **Advised Provincial Health Departments and/or Provincial Pharmacovigilance Centres to take all necessary measures for the implementation of the road map that was agreed by provinces and DRAP for earlier implementation of World Health Organization (WHO) Institutional Development Plans (IDPs) to strengthen the National Regulatory System of Pakistan in respect of pharmacovigilance for the achievement of level 3 status of World Listed Authority (WLA) for Pakistan.**

b. **Balochistan and Sindh should notify their Provincial Pharmacovigilance Centres and share details of the Provincial Focal Person and pharmacovigilance officers from hospitals for the VigiFlow logins. DRAP shall coordinate with these provinces in this regard.**

c. **Provincial Pharmacovigilance Committee (PPVC) should be notified by all provinces (except Punjab) as per Pharmacovigilance Rules, 2022.**

d. **Provincial Pharmacovigilance Centres/Provincial Health Departments should extend the scope of the VigiFlow database to all public and private hospitals of the province.**

e. **Efforts be made to increase awareness and highlight the importance of ADR reporting in public and private healthcare facilities. DRAP should coordinate with provincial health departments and the administration of hospitals for the establishment of hospitals' pharmacovigilance centres, notification of hospital pharmacovigilance committees, the appointment of pharmacovigilance officers at least 1/200 bedded hospital, provision of active clinical role to the pharmacists and subsequent reporting of data to the National Pharmacovigialnce Centre-DRAP.**

f. **National Pharmacovigilance Centre, DRAP shall coordinate with potential private-sector hospitals across the country for the establishment of their pharmacovigilance centres as per Pharmacovigilance Rules, 2022 and provision of VigiFlow logins.**

2. DOMESTIC CASES

2.1. Unintentional mixing of High Alert Medication (HAMs) leading to harm to patients.

i. The provincial Pharmacovigilance Centre, pursuant to the direction of the 14th meeting of the Provincial Pharmacovigilance Committee of the Punjab, held on 29th of October, 2024 recommended the case to the National Pharmacovigilance Centre, DRAP, Islamabad. It was informed that the Provincial Pharmacovigilance Centre (PPC), Punjab received three Therapeutic Goods Related Problem Reports (TGRP) vide No. 1797, 1798, and 1834 regarding the death of patients following the administration of injection Ceftriaxone. Upon investigation, it transpired that the incident occurred, might have been due to the un-intentional mixing of any High Alert Medications (HAMs) such as Lidocaine, Potassium Chloride, and Amiodarone etc. during the reconstitution of the said injection at the nursing station.

ii. After due deliberation and discussion, the Provincial Pharmacovigilance Committee (PVPC) recommended the following proposal for consideration of the DRAP to avoid such incidences in the future:

a. Injection Potassium Chloride should be available in ready-to-use hydration form/pre-diluted solution instead of currently available concentred injection.

b. Distant and standardized branding strategies, including unique colour schemes and labelling should be applied for the critical injectables such as Dextrose 25%, Sodium Bio-carbonate Potassium Chloride etc.

Decision: The PRAEC after detailed discussion and deliberation, decided as follows.-

a) **Agreed with the proposal of Provincial Pharmacovigilance Committee (PVPC), Punjab Pharmacovigilance Centre, Lahore that "*Injection Potassium Chloride should be available in ready-to-use hydration form/pre-diluted solution instead of currently available concentred injection".* As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022, the PRAEC recommended that the Registration Board may take necessary measures with respect to the availability of ready-to-use hydration form/pre-diluted solution of injection Potassium Chloride instead of the currently available concentred injection.**

b) **At the hospital level, measures should be taken to optimize storage practices for concentrated electrolyte injections with round-the-clock monitoring. Likewise, measures should be taken by removing Potassium Chloride from the floor or ward stock/patient bedside and issuance should be through the Pharmacy on patient-need basis with proper labelling, as it will reduce the chances of medication error. The National Pharmacovigilance Centre shall issue advisory to provincial health departments and hospitals in this regard.**

c) **Advised National Pharmacovigilance Centre to prepare a proposal for distinct and standardized branding strategies, including unique colour schemes and labelling for concentrated electrolytes such as Dextrose 25%, Sodium Bio-carbonate and Potassium Chloride etc.**

3. RELIANCE ON INTERNATIONAL SAFETY DECISIONS.

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

i. Tranexamic acid (TXA) is used for the prevention and treatment of haemorrhages due to general or local fibrinolysis in adults and children from one year. Specific indication inter-alia includes gynaecological surgery or disorders of obstetric origin such as postpartum haemorrhage.

ii. Previously, the 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. 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.

iii. 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.

iv. TXA is frequently stored in close proximity to 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.

v. 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 is required in order to decrease this risk, such as storage of TXA away from the anaesthetic drug trolley, preferably outside the theatre

vi. The case was discussed in the 4th meeting of PRAEC, held on 26th of February, 2024 which 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 and the NPC has also issued safety alert in this regard.

vii. To minimise this risk of medication errors, the South African Health Products Regulatory Authority (SAHPRA) has in May 2024 worked with the marketing authorization holders to update the product labelling of tranexamic acid injection to display texts "**HIGH ALERT**" and "**For IV Use Only**" to avoid confusion with other products. In addition, SAHPRA has issued advice for healthcare professionals including:

- Store tranexamic acid injection ampoules separately from other medicines, in a way to avoid reliance on identifying products by the ampoule shape, size, colour, and/or label colour.
- Always check the packaging and ampoule label to ensure the correct product is selected and administered only by a proper route.
- Promptly and visibly label all syringes before use, with the correct product name and route of administration.
- Utilise barcode scanning or a second person to double-check the product label when stocking medication cabinets and preparing medication for injection and before administration.

Decision: The PRAEC decided as per Rule 10 (1) (b) and 10 (1)(h) (vi) of Pharmacovigilance Rules, 2022 and recommended National Pharmacovigilance Centre,-

i. **To issue safety alerts/advisories related to the risk of medication errors due to inadvertent intrathecal Tranexamic acid injection.**

ii. **To coordinate with Provincial Health Departments/Provincial Pharmacovigilance centres and hospitals to enhance the storage practices for tranexamic acid injection at the hospital level along with distinct labelling and double-checking product labels when stocking medication cabinets and preparing medication for injection and before administration to avoid medication error of inadvertent intrathecal administration of tranexamic acid injection.**

3.2. Promethazine hydrochloride injection: Risk of severe chemical irritation and damage to tissues.

i. Promethazine hydrochloride injection is indicated to help manage certain allergic reactions, motion sickness, postoperative nausea and vomiting, and as a sedative or adjunct to analgesics.

ii. The United States Food and Drug Administration (US-FDA) in December 2023 alerted healthcare professionals of labelling updates intended to further reduce the risk of severe chemical irritation and damage to tissues from intravenous administration of promethazine hydrochloride injection.

iii. The FDA recommends healthcare professionals administer promethazine hydrochloride injection by deep intramuscular administration instead of intravenous administration. If promethazine hydrochloride injection must be administered intravenously, healthcare professionals should review and follow the updated information in the labelling to dilute promethazine hydrochloride injection and administer it by intravenous infusion to reduce the risk of severe tissue injury. FDA has required that manufacturers update their prescribing information for promethazine hydrochloride injection to include new safety information and update the carton labelling and container labels with the corresponding information.

iv. If intramuscular injection is not possible, promethazine hydrochloride injection:

- Can be administered intravenously only after dilution, as recommended, and infused through an intravenous catheter inserted in a large vein and preferably through a central venous catheter. Do not administer using intravenous catheters placed into veins in the hand or wrist.
- Should not be mixed with other drugs or diluted with solutions other than 0.9% sodium chloride injection.
- Is contraindicated for intravenous injection at concentrations greater than 1 mg/mL.

v. When diluting and administering promethazine hydrochloride injection by intravenous infusion, infuse over 20 to 40 minutes and follow the below preparation and infusion

instructions in adult and pediatric patients (see the first and second tables below, respectively):

Table 1: Preparation and Infusion Information by Adult Dose of Promethazine Hydrochloride Injection

Dose of Promethazine Hydrochloride Injection	Volume of 0.9% Sodium Chloride Injection for Dilution	Maximum Concentration of the Diluted Promethazine Hydrochloride Injection Solution	Maximum Rate of Infusion
12.5 mg	50 mL	1 mg/mL	2.5 mL/minute
25 mg	50 mL		2.5 mL/minute
50 mg	50 mL		2.5 mL/minute
75 mg	100 mL		5 mL/minute

Table 2: Preparation and Infusion Information by Pediatric Dose of Promethazine Hydrochloride Injection

Dose of Promethazine Hydrochloride Injection	Volume of 0.9% Sodium Chloride Injection for Dilution	Maximum Concentration of the Diluted Promethazine Hydrochloride Injection Solution	Maximum Rate of Infusion
Up to 25 mg	25 mL	1 mg/mL	1.25 mL/minute
25 mg to 50 mg	50 mL		

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders of Promethazine hydrochloride injection should include information related to the risk of severe chemical irritation and damage to tissues when administered through intravenous route as per US-FDA label.**
b. **As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all Promethazine hydrochloride injections in light of the decisions of US-FDA and PRAEC-DRAP.**

3.3. Aripiprazole: Risk of pathological gambling.

i. Aripiprazole belongs to a class of medicines called antipsychotics. Aripiprazole has 3 approved indications: treatment of schizophrenia in adults and adolescents aged over 15 years; short-term treatment of moderate to severe manic episodes in Bipolar I disorder in adults and adolescents aged 13 years and older; and prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

ii. The Medicines and Healthcare Products Regulatory Agency (MHRA) in December 2023 reminded healthcare professionals prescribing aripiprazole to be alert to the known risk of patients developing addictive gambling, following a rise in the number of reports received in 2023.

iii. The MHRA informed that from 30 June 2009 to 28 August 2023, it has received 69 Yellow Card reports citing aripiprazole as a suspect medicine for the side effects of gambling or gambling disorder. Across the 69 reports of gambling and gambling disorders, most reports concerned people aged 20 to 40 years, although there were reports of patients up to 60 years of age. In many cases, the patients had no previous history of gambling behaviour. In the majority of cases, cessation of aripiprazole led to a marked reduction or total loss of impulses to gamble.

iv. It was informed that it has been noted since the beginning of 2023, there has been an increased number of Yellow Card reports for aripiprazole which include gambling, gambling disorder or obsessive-compulsive disorder in the United Kingdom. A review of the available evidence was considered by the Neurology, Pain and Psychiatry Expert Advisory Group (NPPEAG) of the Commission on Human Medicines (CHM). The NPPEAG noted that the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) for aripiprazole contain information regarding pathological gambling and other impulse control disorders. The SmPC states that impulse control disorders may result in harm to the patient and others, if not recognised and advises consideration of dose reduction or stopping the medication if a patient develops increased urges while taking aripiprazole. In reviewing this issue, the NPPEAG recommended that the MHRA remind healthcare professionals and patients of these risks.

Decision: The PRAEC decided as per Rule 10(1)(b) and Rule 10(1)(h)(vi) of the Pharmacovigilance Rules, 2022 and recommended the National Pharmacovigilance Centre to issue a safety alert to inform healthcare professionals and patient to be alert to the known risk of developing addictive gambling with Aripiprazole.

3.4. Cefotaxime: Risk of severe cutaneous adverse reactions (SCARs).

i. *Cefotaxime* is an injectable third-generation cephalosporin antibiotic used to treat a variety of bacterial infections.

ii. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) in its January 2024 meeting recommended updating the product information (Warnings and Precautions and Adverse Drug Reaction sections) for cefotaxime, to include the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) and to strengthen advice on severe cutaneous adverse reactions (SCARs) including DRESS.

iii. The updated product information's undesirable effect of Cefotaxime should list Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) as an ADR with frequency "Not known".Whereas, the warnings and precautions section for cefotaxime should state the following:

- SCARs including acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS, which can be life-threatening or fatal, have been reported post-marketing in association with cefotaxime/ethambutol treatment.

- At the time of prescription patients should be advised of the signs and symptoms for skin reactions.

- If signs and symptoms suggestive of these reactions appear, cefotaxime/ethambutol should be withdrawn immediately.

- If the patient has developed AGEP, SJS, TEN or DRESS with the use of cefotaxime/ethambutol, treatment with cefotaxime/ethambutol must not be restarted and should be permanently discontinued.

- In children, the presentation of a rash can be mistaken for the underlying infection or an alternative infectious process, and physicians should consider

the possibility of a reaction to cefotaxime/ethambutol in children who develop symptoms of rash and fever during therapy with cefotaxime/ethambutol.

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, that registration holders should include information related to severe cutaneous adverse reactions (SCARs) in the warning and precaution section of the prescribing information/label of cefotaxime and also list the Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) as an ADR with frequency "Not known" in the prescribing information.**

b. **As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all cefotaxime medicines in light of the decisions of PRAC-EMA and PRAEC-DRAP.**

3.5. Ezetimibe: Risks of Drug-Induced Liver Injury (DILI) and Severe Cutaneous Adverse Reactions (SCARs)

i. Ezetimibe is a cholesterol absorption inhibitor and is indicated, as an adjunct to diet and lifestyle changes when the response to these and other non-pharmacological measures alone has been inadequate, for the treatment of primary hypercholesterolemia, homozygous familial hypercholesterolemia and homozygous sitosterolemia (phytosterolemia).

ii. Health Canada in March 2024 has updated the product information for ezetimibe (Ezetrol®) to include warnings about serious adverse reactions including drug-induced liver injury (DILI) and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilic and systemic symptoms (DRESS).

iii. The marketing authorization holder conducted a review of international safety data and the scientific literature and identified 42 post-marketing cases of DILI in patients taking ezetimibe. There was sufficient evidence to suggest a causal association between ezetimibe monotherapy and DILI. Therefore, the current recommendation to consider performing liver function tests at the initiation of, or during treatment with, ezetimibe in combination with a statin or fenofibrate has been expanded to include ezetimibe monotherapy. The review also identified rare cases of SCARs in patients taking Ezetrol. There was sufficient

evidence to suggest at least a reasonable possibility of a causal association with some cases of SJS, TEN, and DRESS.

iv. Healthcare professionals were advised to consider performing liver function tests at the initiation of Ezetrol, whether administered as monotherapy or in combination with a statin or fenofibrate and subsequently as required. Instruct patients to immediately contact a healthcare professional if they experience symptoms of liver injury. Liver function should be evaluated if liver injury is suspected. Instruct patients to stop taking Ezetrol and to seek immediate medical help if they experience symptoms of SCARs.

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders should include warnings about serious adverse reactions including drug-induced liver injury (DILI) and severe cutaneous adverse reactions (SCARs) to the prescribing information of Ezetimibe containing medicines (monotherapy or in combination) in the adverse drug reaction and warning and precaution sections.**

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

3.6. Chlorhexidine (cutaneous use): Risk of persistent corneal injury and significant visual impairment.

i. Chlorhexidine is an antiseptic and disinfectant, which is used for skin disinfection before surgery and and is applied to the umbilical cord stump during the first week of life for newborns who are born at home in settings with high neonatal mortality (neonatal mortality rate >30 per 1000).

ii. The PRAC of the EMA in its April, 2024 meeting has recommended updating the product information for chlorhexidine for cutaneous use, indicated for skin disinfection, and relevant combination products to include the risk of persistent corneal injury and significant visual impairment. Cases of severe corneal erosion and permanent significant visual impairment due to inadvertent ocular exposure have been reported in the post-marketing phase, leading to some patients requiring corneal transplants.

iii. The PRAC agreed that all MAHs of chlorhexidine monocomponent and fixed-combination-containing products indicated for skin disinfection and intended for cutaneous use should update the product information. The warning and precaution sections of the product information for the relevant chlorhexidine products should state:

- This product must not come into contact with the eye.
- Serious cases of persistent corneal injury, potentially requiring corneal transplant, were reported following accidental ocular exposure to chlorhexidine-containing medicinal products despite taking eye protective measures due to migration of solution beyond the intended surgical preparation area.
- Extreme care must be taken during application to ensure that this product does not migrate beyond its intended application site into the eyes. Particular care should be taken in anaesthetised patients, who are unable to immediately report ocular exposure.
- If this product comes into contact with the eyes, wash out promptly and thoroughly with water. An ophthalmologist's advice should be sought.

iv. The PRAC also recommended updating the undesirable effect section of production information by listing Corneal erosion, epithelium defect/corneal injury, and significant permanent visual impairment as frequency "not known".

v. Previously, the World Health Organization (WHO) in August 2020 issued an alert about multiple reports of administration errors causing eye injuries, such as blindness, following incorrect route of administration of chlorohexidine gluconate (CHX) to the eyes instead of to the umbilical cord in newborns.

vi. Clean, dry cord care is recommended for newborns born in health facilities, and at home in low neonatal mortality settings. The use of chlorhexidine in these situations may be considered only to replace the application of a harmful traditional substance such as cow dung to the cord stump. The use of CHX is being implemented in many countries (South Asia and sub-Saharan Africa) as part of a package of essential newborn interventions to reduce the incidence of omphalitis. It is also listed in the WHO Essential Medicines List.

vii. CHX causes serious harm if mistakenly applied to the eyes, resulting in severe eye injuries. Over forty (40) cases of such incorrect administration have been recorded, either as media

reports or in the literature, since 2015. Injuries associated with both the liquid and gel (ointment) formulations have been reported when CHX was mistaken for eye drops or ointments. All healthcare professionals, caregivers and others involved in the distribution, use and/or administration of chlorohexidine 4% gel or solution, are advised to take all necessary measures and precautions to ensure its correct use and administration.

viii. The following suggestions were recommended to National Neonatal and Reproductive Health Programmes and/or Regulators include the following:

- Assess what products are part of the newborn package and select the optimal primary container/dosage form for CHX or modify the design of the container to distinguish the product from other medicines typically used for newborns.
- Update the product label with appropriate information on the safe use of the product.
- Develop more detailed instructions for users (flyers, posters, pictorials etc.) that are culturally appropriate and easy to understand, to ensure correct use of the product.
- Train healthcare professionals who interact with mothers and/or provide the product to ensure a full understanding of the indications and contraindications for use and application methods.

ix. All stakeholders were advised to remain alert to incidents of eye injury with CHX in their settings and to report these to their National Regulatory Authority (NRA). Member States are reminded that adverse events associated with the use of any medicinal product should be reported to the National Regulatory Authority.

Decision: The PRAEC decided as follows:-

a. As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 decided that registration holders should update the warning and precaution sections of chlorhexidine monocomponent and fixed-combination-containing products indicated for skin disinfection as well as to list Corneal erosion, epithelium defect/corneal injury, and significant permanent visual impairment as frequency "not known" in the ADR section.

b. **As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all chlorhexidine monocomponent and fixed-combination-containing products in light of decisions of EMA-PRAC, WHO and PRAEC-DRAP.**

c. **DRAP should coordinate with provincial health departments for onward coordination with hospitals to ensure that proper protective equipment are being used by persons handling chlorhexidine along with hospital labelling of "irritating agent" and include this product in the material data safety sheet.**

3.7. 17-Hydroxyprogesterone caproate (17-OHPC): Suspension of marketing authorisations.

i. 17-hydroxyprogesterone caproate (OHPC) is a synthetic progesterone (a steroid hormone that acts like progesterone). In some EU countries, 17-OHPC medicines are authorised as injections to prevent pregnancy loss or premature birth in pregnant women. They are also authorised for the treatment of various gynaecological and fertility disorders, including disorders caused by a lack of progesterone.

ii. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in May, 2024 recommended the suspension of the marketing authorisations for medicines containing 17-hydroxyprogesterone caproate (17-OHPC). The PRAC reviewed the results of a large population-based study, which looked at the risk of cancer in people who had been exposed to 17-OHPC in the womb, over a period of about 50 years from the time they were born. Data from this study suggest that these people might have an increased risk of cancer compared with those who were not exposed to the medicines. However, the PRAC noted that there was a low number of cancer cases in the study and that the study had some limitations, such as limited information on risk factors for cancer. The PRAC therefore concluded that the risk of cancer in people exposed to 17-OHPC in the womb is possible, but cannot be confirmed due to uncertainties. On 26 June 2024, the CMDh endorsed the recommendation from EMA's safety committee, PRAC, to suspend the marketing authorisations for medicines containing 17-hydroxyprogesterone caproate (17-OHPC) in the European Union (EU).

iii. In its review, the PRAC also considered data on the effectiveness of 17-OHPC medicines in their authorised uses, including the results from a study looking at how well they

prevented premature birth. The study, which involved over 1,700 pregnant women with a history of preterm delivery, found that 17-OHPC is no more effective than a placebo (a dummy treatment) in preventing recurrent premature birth or medical complications due to prematurity in newborns. The Committee also reviewed two published meta-analyses (combined analyses of multiple studies), which confirmed that 17-OHPC is not effective at preventing preterm birth. For the other authorised uses of 17-OHPC, the PRAC concluded that there is limited evidence of effectiveness.

iv. In addition, the review considered new studies which showed that 17-OHPC is not effective in preventing premature birth; there are also limited data on its effectiveness in other authorised uses. In view of the concern raised by the possible risk of cancer in people exposed to 17-OHPC in the womb, together with the data on the effectiveness of 17-OHPC in its authorised uses, the PRAC considered that the benefits of 17-OHPC do not outweigh its risks in any authorised use. The Committee therefore recommended the suspension of the marketing authorisations for these medicines. Alternative treatment options are available.

v. Previously, the US-FDA, in April 2023 announced the final decision to withdraw approval of Makena (Hydroxyprogesterone caproate)—a drug that had been approved under the accelerated approval pathway. This drug was approved to reduce the risk of preterm birth in women pregnant with one baby who has a history of spontaneous preterm birth. The decision was issued jointly by the FDA Commissioner and Chief Scientist. The FDA approved Makena (Hydroxyprogesterone caproate)— under the accelerated approval pathway in 2011 based on a determination that the sponsor had demonstrated a drug effect on an intermediate clinical endpoint that was reasonably likely to predict clinical benefit. The agency's approval included a requirement that the sponsor conduct a post-marketing confirmatory study. The ensuing confirmatory study did not verify clinical benefit and the FDA's Center for Drug Evaluation and Research (CDER) proposed withdrawing the drug's approval in 2020. The sponsor requested a hearing, which was held in October 2022. Following the hearing, the FDA Commissioner and Chief Scientist reviewed the record for this matter, including the submissions by CDER and sponsor Covis Pharma, public comments to the docket, the transcript of the hearing and the Presiding Officer's report. Based on that review, they have decided to withdraw approval of Makena and generic

versions of Makena. Approvals of these drugs have been withdrawn because the drugs are no longer shown to be effective and the benefits do not outweigh the risks for the indication for which they were approved.

Decision: The PRAEC after detailed deliberation and in light of the benefit-risk assessment of the US-FDA and EMA-PRAC decided as follows,-

a) As per Rule 10 (1) (h) (v) of the Pharmacovigilance Rules, 2022 to suspend the 17-hydroxyprogesterone caproate (17-OHPC) in Pakistan due to risk of cancer in people exposed to 17-OHPC in the womb together with its effectiveness in its authorised uses wherein benefits of 17-OHPC do not outweigh its risks in any authorised use.

b) As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to suspend the registration of hydroxyprogesterone caproate (17-OHPC) containing medicine in Pakistan in light of decisions of EMA-PRAC, US-FDA and PRAEC-DRAP.

3.8. Sorafenib - Potential Risk of Tumour Lysis Syndrome.

i. Nexavar is a prescription drug for the treatment of liver cancer (hepatocellular carcinoma) that cannot be treated by surgery, late-stage kidney cancer (renal cell carcinoma) and late-stage thyroid cancer (thyroid carcinoma).

ii. In its safety review reports issued through the Infowatch Newsletter (June 2024 issue), Health Canada informed about the potential risk of Tumor lysis syndrome (TLS) with the use of Nexavar. The safety review was triggered by a labelling update made by the EMA and international case reports published in the medical literature. Health Canada reviewed information provided by the manufacturer, and from searches of the Canada Vigilance database, international databases and the scientific literature. Health Canada reviewed 9 international cases of TLS in patients taking sorafenib, including 8 from the published literature. All 9 cases were found to be possibly linked to the use of sorafenib, although a potential contribution from spontaneous TLS (cancer cell breakdown in the absence of treatment) could not be ruled out. The reported time to the onset of TLS ranged from 3 to 34 days after starting treatment with sorafenib. Five deaths were reported among the 9 cases assessed. All 5 deaths were found to be possibly linked to TLS from sorafenib treatment. However, other causes of death, such as cancer progression, could not be ruled

out. Health Canada reviewed 1 additional article published in the scientific literature, A link between sorafenib and TLS could not be established due to study limitations. Health Canada concluded the review and found a possible link between the use of Nexavar and the risk of TLS. Health Canada is working with the manufacturer to update the CPM for Nexavar to include the risk of TLS.

iii. Tumor lysis syndrome is a potentially life-threatening condition that can occur during cancer treatment. When cancer cells are killed by the cancer treatment, they release their contents (salts and proteins) into the blood. When cancer cells break down faster than the kidneys can remove these substances from the blood, it can cause changes to the chemical balance in the blood, which may result in damage to organs, most commonly the kidneys, heart and brain.

iv. Previously, the PRAC-EMA in its February 2022 meeting, considered the available evidence, including the data submitted by the MAH (Bayer AG), and recommended including the following information in the warning and precaution sections of Sorafenib.- "*Cases of TLS, some fatal, have been reported in postmarketing surveillance in patients treated with sorafenib. Risk factors for TLS include high tumour burden, pre-existing chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine. These patients should be monitored closely and treated promptly as clinically indicated, and prophylactic hydration should be considered.".* Likewise, the PRAC also recommended listing tumour lysis syndrome in the ADRs section with the frequency 'not known'.

Decision: The PRAEC decided as follows:-

a. **As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders should update the product information of Sorafenib by including information about the risk of tumour lysis syndrome (TLS) in the warning and precaution section and also to list TLS in the adverse drug reaction section with "unknown" frequency.**

b. **As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all Sorafenib-containing medicines in light of decisions of Health Canada, EMA-PRAC and PRAEC-DRAP.**

3.9. Medroxyprogesterone Acetate: Risk of meningioma

i. Medroxyprogesterone acetate are medicine which are used for gynaecological (including contraception and endometriosis) and oncological indications.

ii. The Pharmacovigilance Risk Assessment Expert Committee (PRAC) of the European Medicine Agency (EMA) in its meeting of September 2024, recommended measures to minimise the risk of meningioma, a type of brain tumour, with medicines containing medroxyprogesterone acetate.

iii. Meningiomas are tumours of the tissue layer surrounding the brain and spinal cord. Usually, they are benign (non-cancerous) and grow slowly but, depending on the size or location, they can cause serious problems.

iv. The committee's recommendations followed a review of data from epidemiological studies, case studies from the medical literature and cases reported in the pharmacovigilance database of the European Union. These data show an increased risk of meningioma in people taking high doses of medroxyprogesterone acetate (injectables and ≥100 mg tablets) for several years. Although the relative risk of meningioma is significantly increased with the use of high-dose medroxyprogesterone acetate, the absolute risk is very small.

v. The PRAC recommended that, in patients who have a meningioma or have had one in the past, medicines containing high-dose medroxyprogesterone acetate must not be used, unless medroxyprogesterone acetate is needed for the treatment of an oncological indication. The PRAC also recommended that patients taking high doses of medroxyprogesterone should be monitored for symptoms of meningioma, which can include vision change, hearing loss or ringing in ears, loss of smell, headaches, memory loss, seizures and weakness in arms and legs. If a patient treated for a non-oncological indication is diagnosed with meningioma, treatment with high-dose medroxyprogesterone acetate must be stopped. If a patient treated for an oncological indication is diagnosed with meningioma, the need for further treatment with high-dose medroxyprogesterone should be carefully considered, on a case-by-case basis, taking into account individual benefits and risks.

vi. Likewise, in its safety review reports issued through Infowatch (October 2024 issue), Health Canada informed that warnings and precautions and patient medication information sections of the Canadian product monographs of medicine containing medroxyprogesterone acetate have been updated with the risk of meningioma. It was also informed that meningiomas have been reported following long-term administration of progestins, including medroxyprogesterone acetate (MPA) and it should be discontinued if a meningioma is diagnosed. Caution is advised when recommending medroxyprogesterone to patients with a history of meningioma.

Decision: The PRAEC decided as follows:-

c. As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, that registration holders should update the product information of medicine containing medroxyprogesterone acetate (MPA) by including information about the risk of "meningioma" in the warning and precaution section.

d. As per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of all medroxyprogesterone acetate-containing medicines in light of decisions of EMA-PRAC, Health Canada and PRAEC-DRAP.