MINUTES OF 3RD MEETING OF PHARMACOVIGILANCE RISK ASSESSMENT EXPERT COMMITTEE

The National Pharmacovigilance Centre, Division of Pharmacy Services, Drug Regulatory Authority of Pakistan
File No: 17-3/2023-PRAEC(PS)

SEPTEMBER 8, 2023
DRUG REGULATORY AUTHORITY OF PAKISTAN
Telecom Foundation Complex, 7th Mauve Area, G-9/4, Islamabad

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Minutes of the 3rd meeting of the Pharmacovigilance Risk Assessment Expert Committee.

The 3rd 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 8th of September, 2023. 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. (R) 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. Arifullah Khan, Dean, Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad.	Member
5	Mr Shoukat Sahad, Chief Pharmacist, Rehman Medical Institute (RMI), Peshawar.	Member
6	Mr Taimoor Chaudhary, Section Supervisor (Drug Chemistry Unit), Punjab Forensic Science Agency, Lahore.	Member
7	Dr Khalid Mehmood, Associate Prof./Head of Pharmacy, Department of Pharmacy, Abbottabad University of Science & Technology, Abbottabad.	Member

Mr Abdul Mateen, Deputy Director / Secretary presented the agenda. Mr Malik Muhammad Asad Deputy Director and Mst. Aqsa Hashmi, Deputy Director assisted the Secretary PRAEC in the presentation of the agenda and preparation of minutes.

1. Miscellaneous Items.

1.1. Confirmation of minutes of 2nd meeting of PRAEC.

i. The 2nd meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held on the 7th of March, 2023. The draft minutes of the meeting were prepared and shared with expert members through email and were finalized in light of the emails of members on 16-03-2023.

ii. Accordingly, as per minutes of the 2nd meeting of PRAEC, the safety alerts were issued and decisions were communicated to the concerned Divisions of the DRAP.

iii. The minutes of the 2nd meeting are 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 2nd meeting of PRAEC held on the 7th of March, 2023.

1.2. Strengthening of Pharmacovigilance activities in the country.

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. The World Health Organization (WHO) in its recent formal benchmarking of Pakistan's National Regulatory System 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.

ii. The Pharmacovigilance Risk Assessment Expert Committee (PRAEC) in its 2nd meeting decided to interact with focal persons of pharmacovigilance of each Province, Azad Jammu & Kashmir, Gilgit Baltistan and ICT to review the existing pharmacovigilance system at the National and Provincial level.

iii. The meeting was attended by the following focal persons from the provinces.

a. Sardar Shabbir Ahmed, Focal Person Pharmacovigilance, Islamabad.

b. Dr Shabana Junejo, Focal Person Pharmacovigilance Sindh, Additional Medical Superintendent, Dr Ruth K.M Pfau, Civil Hospital, Karachi.

c. Mst. Nusrat Rehman, Director, Pharmacovigilance, Directorate of Drugs Control, Punjab, Lahore.

d. Mr Fazal Haq, Focal Person Pharmacovigilance, Drug Control and Pharmacy Services, Peshawar.

A. Updates from the National Pharmacovigilance Centre:

Dr Obaidullah, Head of the National Pharmacovigilance Centre (NPC)/ Director, Division of Pharmacy Services delivered a presentation regarding pharmacovigilance activities in the country and specifically highlighted the following points:

a. The evolution of the pharmacovigilance system in Pakistan during the period 1994-2023, role and responsibilities of national, provincial and regional pharmacovigilance centres as per Pharmacovigilance Rules, 2022, the institutional development plans identified by WHO in pharmacovigilance field visits during recent benchmarking, and the proposed way forward including the notification of provincial centres and committee, strengthening of human resources at all levels and adoption of uniform ADRs collection system i.e VigiFlow from the hospitals.

b. The National Pharmacovigilance Centre, DRAP has launched its quarterly Pharmacovigilance Newsletter (Issue No.01, Volume 1, September, 2023). Its objectives include educating stakeholders on medication safety, encouraging the spontaneous reporting of ADRs in Pakistan etc. The newsletter also includes valuable information on the detection, assessment, understanding and prevention of adverse effects related to medications.

c. To further improve pharmacovigilance reporting, Uppsala Monitoring Centre has accepted NPC's request for provision of unlimited dedicated VigiFlow logins to healthcare professionals at regional (provincial) centres and sub-regional centres at the hospital level. The purpose of the VigiFlow decentralization is to lower the burden of data entry on the provincial and national centres so that they can focus on the other activities of signal detection and management etc.

B. Updates from Islamabad Pharmacovigilance Centre:

Sardar Shabbir Ahmed, SQCB/Focal Person for Pharmacovigilance, Islamabad briefed the Committee about the development and progress of the Pharmacovigilance Centre, Islamabad as per the following details:

a. He informed that Islamabad being the 2nd Regional PV Centre in the country started its activities in 2019 with notification of PV Centre for Islamabad and its Focal Person.

b. MoUs have been were signed with fourteen major hospitals for ADR reporting. This was followed by capacity building and training of the nominated focal persons of the hospitals with the support of the Pharmacy Services Division of DRAP. Consequently, ADR reporting forms and reporting format were shared with all and a dedicated WhatsApp group and email is operational for better coordination and reporting.

c. After notification of the Pharmacovigilance Rules, 2022, the focal person was again notified by the Ministry of Health as required under the Rules and accordingly, one of the Drug Inspectors of the Health Department, Islamabad was nominated as Pharmacovigilance Officer.

d. Currently, the ADR data is shared by four private sector hospitals in Islamabad which is being entered in VigiFlow on a regular basis and so far 311 ADRs have been shared with NPC. In addition, the Islamabad PV Centre is strengthening its coordination with the remaining private and public-sector hospitals of Islamabad so that ADR reporting can also be initiated from within these hospitals. A meeting with the EDs of the public sector hospitals is also in the schedule to develop an ADR reporting mechanism.

e. It was further apprised by the officer that a Public Sector Development Programme (PSDP) project titled "*Strengthening of the Drug Control Section of the Islamabad Health Department"* has been approved by the Department Development Working Party (DDWP) where the establishment of a dedicated Pharmacovigilance Centre for ICT has been incorporated as an integral component. Recruitment of 03 dedicated Pharmacovigilance Officers along with staff and required logistics shall be kicked off soon under the said PSDP project which shall be instrumental in the development of a robust PV centre in Islamabad with all required facilities.

C. Updates from Punjab Pharmacovigilance Centre:

Mst. Nusrat Rehman, Director, Pharmacovigilance, Directorate of Drugs Control, Punjab, Lahore and Mst Aqsa Iftikhar, Assistant Director presented the updated status of pharmacovigilance activities in Punjab as per the following details:

a. Punjab has dedicated Clinical Pharmacy and Pharmacovigilance Officers (CPPO) in Tehsil Headquarters and District Headquarters public sector hospitals and also in specialized tertiary care public sector hospitals.

b. The Punjab has a dedicated notified Pharmacovigilance Committee and also regularly issues safety alerts and Newsletters.

c. The active reporting is from public sector hospitals and reports are collected through a medicines surveillance system (MSS). Likewise, there is a drug and device complaint (DDC) form designed for point of sale where the general public and healthcare professionals can report. Suspected ADRs reporting of NPC is also shared with CPPOs for collection of reports from wards.

d. It was suggested that the provision of VigiFlow logins should be started with a pilot project where the logins should be initially provided in 3-5 major reporting hospitals.

D. Updates from Khyber Pakhtunkhwa Pharmacovigilance Centre:

Mr Fazal Haq, the Focal Person of Pharmacovigilance of Khyber Pakhtunkhwa shared the following information:

a. Summary of the notification of the Provincial Pharmacovigilance Centre, Pharmacovigilance Committee and Pharmacovigilance Officers is in the approval phase.

b. About 15-20 focal persons from public and private hospitals and the Pharmacovigilance programme have been identified and will start relevant activities after the notification of the Pharmacovigilance Centre.

E. Updates from Sindh:

Dr Shabana Junejo, the Focal Person of Pharmacovigilance Sindh shared the following information;

a. No dedicated human resources and infrastructure for the pharmacovigilance system in Sindh.

b. There is a need for capacity building and the provision of logins at the primary level so that data can be collected actively.

Discussion: Members of PRAEC appreciated the steps taken at provincial levels for the development and promotion of pharmacovigilance activities. However, for effective implementation of pharmacovigilance activities, members proposed the following suggestions:

i. Human resources should be further strengthened before the initiation of the provision of VigiFlow logins and adequate capacity building regarding the use of the aforementioned software.

ii. Implementation of pharmacovigilance activities should be time-bound and there should be frequent follow-up meetings.

iii. The need for a National Dialogue and conference for confidence building and awareness of ADR reporting was emphasised.

iv. National Pharmacovigilance should issue a regular Newsletter and raise awareness through social and print media.

v. The Medical Superintendents of public sector hospitals should be sensitized for ADRs reporting in the hospital and its role in patient safety at large.

vi. Adequate measures for capacity building and training at the provincial level.

vii. Coordination should be carried out with hospitals, universities and pharmacy councils so that final-year Pharm-D students should have a supportive role in the awareness of pharmacovigilance activities and the collection of ADRs reports in hospitals.

Decision: PRAEC after detailed deliberation decided as follows:

a. Health departments of each province, territory and state should nominate their focal persons (if not nominated yet) and notify their pharmacovigilance centres, committee and pharmacovigilance officers as per Pharmacovigilance Rules, 2022.

b. A uniform ADR collection tool i.e. VigiFlow needs to be adopted at the National, Provincial and hospital levels. As a pilot project, Provincial Pharmacovigilance Centres/ Health Departments will initially share details of 3-5 pharmacovigilance officers from major reporting hospitals for granting access to VigiFlow logins. After the successful implantation of the aforementioned pilot project, necessary training will be imparted and VigiFlow logins will be provided to all hospitals for uniform reporting across the country.

c. DRAP and respective health departments will further strengthen pharmacovigilance units by increasing the number of human resources and infrastructure at the respective National, Provincial and hospital levels.

d. 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.

e. Efforts will be made to increase awareness and highlight the importance of ADR reporting in public and private healthcare facilities.

f. Provincial Pharmacovigilance focal persons who couldn't attend the meeting will be invited in the next PRAEC meetings to present the updated status in their respective areas.

1.3. Therapeutic Inefficacy/Treatment Failures due to Antimicrobial Resistance:

i. The prevalence of infectious diseases in humans and animals is becoming even more persistent due to the growing resistance in microbes against the limited antimicrobials available in the market. The antimicrobials that are discovered after years of research are misused and overprescribed rendering these ineffective in a very short time. As a healthcare community, it is the shared responsibility to eradicate such and other factors adding to AMR and take measures for preventing future infections from becoming untreatable.

ii. Recently a few concerns have been raised over the increasing resistance to antibiotics in critical infection cases putting lives at risk of death and disability.

Concerns Raised by Holy Family Hospital:

1. Common prevalence of resistant strains like Klebsiella pneumonia, E-coli, Pseudomonas aeruginosa and acinetobacter, with sensitivity to injections Colistimethate Na and Tigecycline (unsafe for paediatric use).
2. PAN-resistant strains of Serratia marcescens (cause of meningitis in children).
3. Resistance of common infections to 3rd generation antibiotics.
4. Complexity in treatment of cases of infectious diseases referred to tertiary care hospitals from primary health facilities, private hospitals and clinics. The major underlying factor

of this issue is the lack of restricted antibiotic use as given in the form of the AWaRe classification given in NEML and WHO-MLEM.

5. Some of the antibiotics of concern are moxifloxacin, teicoplanin, linezolid, azithromycin, piperacillin+tazobactam, meropenem, imipenem+cilastatin, cefoperazone+salbactam.
6. Some cases of PAN-resistant and 4th-generation antibiotics resistant cases have also been provided.

Discussion:

i. The issue raised requires to be addressed based on the two components i.e. antimicrobial resistance (AMR) and antimicrobial consumption surveillance (AMC) for which NIH and DRAP are the focal points respectively. DRAP although sharing the responsibility of antimicrobial stewardship is striving to contribute significantly for AMC surveillance.

ii. An exercise of tailoring the antimicrobials AWaRe List of NEML was carried out earlier this year in the context of Pakistan's antimicrobial resistance and sensitivity patterns. The list has been finalized but the outline of the document is yet to be finalized and provided by the consultants engaged by WHO Pakistan.

iii. AMR like other LMICs has a high prevalence in Pakistan. According to the report published in 2022 by Fleming Fund Country Grant Pakistan "The Antibiotic Footprint Analysis: Antibiotic Consumption by Human and Animal Health Sectors in Pakistan During 2019" the numbers indicating the use of antimicrobials is alarming. 12.5% of this use consists of the unregulated off-label use of antimicrobials as growth promoters (in feed additives) for poultry, being imported under the category of feed/feed premixes and therefore getting unhindered clearance from customs. This is a major contributor to AMR in Pakistan as microbes can develop resistance on exposure to these sub-therapeutic levels/residues of antimicrobials present in the food from animal sources that we consume. Keeping in view the importance of the matter, the Pharmacy Services Division has already placed an agenda for the consideration of the Authority for deliberation with a way forward of coordination with the Animal Husbandry Commissioner and the Customs to ban the import of growth promoters or feed premixes containing antimicrobials.

iv. The practice of General Physicians also cannot be ignored as watch and reserve class antimicrobials are being frequently prescribed in very mild infections which are rendering the more serious ones like typhoid into MDR and XDR cases hence untreatable.

v. The situation of public sector hospitals is dire lacking a Pharmacy and Therapeutic Committee and the existence of antimicrobial stewardship programmes is only somewhat evident in major private sector hospitals. Many such hospitals with the Pharmacy and Therapeutic Committees in place, have a regular meeting agenda wherein it is required to present antimicrobials utilization and antibiograms of the hospital. This activity brings to light the situation with evidence and information for any implementable actions, decisions or advice.

vi. The reports shared by Holy Family Hospital present a grave situation of many multiple resistance strains and therapeutic failures. The level of resistance of antimicrobials in Pakistan is more than 50% and it is increasing by the day, with the added threat of leaving us devoid of any treatment for bacterial infections. Publication of antibiograms and local data at the hospital or regional level has a significant role which can help policymakers and decision-making bodies to take concrete steps.

vii. The matter requires elaborative thinking and the development of an implementable strategy taking into account the situation of public sector hospitals and the available resources. DRAP requires time to consult the relevant stakeholders and come up with a document which is adaptable and provides adequate guidance.

Decision: PRAEC after detailed deliberation decided as follows:

i. Division of Pharmacy Services to prepare a comprehensive proposal related to anti-microbial consumption surveillance and antibiotic stewardship programme.

ii. Follow up regarding notification of classification of AWaRe list and then issuance of advisories and recommendations to provincial health departments for amendment in Drug Sale Rules for sale of antibiotics on prescription only.

iii. Inclusion of anti-biotic in risk-based post-marketing surveillance plan by the QA& LT Division, DRAP.

iv. Coordination with the National Institute of Health (NIH) to explore the possibility of developing anti-biograms for different areas/ cities.

2. Reliance on International Safety Decisions.

2.1. Fluoropyrimidines: Risk of potentially life-threatening toxicity in di-hydropyrimidine dehydrogenase (DPD) deficient patients.

i. The Therapeutic Goods Administration (TGA) of Australia in Sep-2022 and the Medicine and Health Product Agency (MHRA) in Oct, 2020 issued updates regarding the use of fluorouracil and its prodrugs capecitabine and flucytosine. These updates included a new warning about the potential for severe and life-threatening toxicity in patients with a partial di-hydropyrimidine dehydrogenase (DPD) deficiency. Previously, these medications were contraindicated for patients with known complete DPD deficiency. Reports of adverse events suggested a link between DPD deficiency and toxicities, although DPD deficiency testing was often not performed in affected patients. Healthcare professionals were advised to consider DPD deficiency testing before initiating therapy and to reduce the starting dose if partial DPD deficiency is detected. Similar recommendations were made by the MHRA, referencing a European safety review, which emphasized the importance of DPD deficiency testing prior to treatment initiation. Testing is not required for topical fluorouracil formulations due to minimal systemic absorption. The PRAC of the EMA in March 2020 also recommended pre-treatment testing for DPD deficiency before administering fluorouracil and its prodrugs via injection or infusion. Lack of DPD enzyme can lead to the accumulation of fluorouracil in the blood, resulting in severe and life-threatening adverse reactions. Patients with complete DPD deficiency should not be given these medications, and a reduced starting dose is recommended for patients with partial DPD deficiency.

ii. The case was discussed in the 2nd meeting of PRAEC, wherein it was decided to Co-opt experts in Oncology as per Rule 9 (5) of the Pharmacovigilance Rules, 2022 to assess the case of testing of DPD deficiency in patients before initiation of treatment with Fluorouracil and Capecitabine and submit their reports in the next meeting of PRAEC. Accordingly, the following two members were co-opted and were requested to present their reports in this meeting:
    - Dr Munira Shabbir Moosajee, Clinical Associate Professor & Section Head, Medical Oncology, Director – Bone Marrow Transplant Program, Department of Oncology, Agha Khan University Hospital, Karachi.
    - Dr Kausar Bano, Associate Professor, Jinnah Hospital, Lahore.

Discussion:

a. Dr Munira Shabbir Moosajee informed that testing of testing for DPD deficiency before Fluoropyrimidines treatment is not a mandatory recommendation by some agencies as there is racial variation concerning its deficiency. As per the 2020 article of the American Society of Clinical Oncology (ASCO), the prevalence of complete and partial deficiency percentage of DPD in the Pakistani population is very low. In Agha Khan Hospital, 1-2 patients are being suspected in a year of DPD deficiency and there is no reported toxicities-related death. Furthermore, DPD deficiency tests are not available in Pakistan and cannot be carried out for each patient. However, DPD-deficient patients could be suspected by doctors in his/her practice. Therefore, it would be better to include information about the contraindications to complete DPD deficient patients and reduce the starting dose in partial patients in the prescribing information.

b. Dr. Kausar Bano agreed with Dr. Munira regarding the prevalence of racial variation of DPD-deficient patients. It was informed that DPD-related toxicity is not common in Pakistan. Furthermore, if tests are being made available in Pakistan the cost and time taken for these tests may hamper the benefit of the provision of treatment with Fluoropyrimidines for cancer patients.

Decision: The PRAEC decided as follows:

a. As per Rule 10(1)(h)(ii) of the Pharmacovigilance Rules, 2022 recommended registration holders to update of contraindications in patients with a known complete absence of di-hydro pyrimidine dehydrogenase (DPD) activity.

b. As per Rule 10(1)(h)(iv) of the Pharmacovigilance Rules, 2022 recommended registration holders to update the warning and precaution section by including information about the importance of testing for DPD deficiency before initiation of the treatment with Fluoropyrimidines (Fluorouracil and Capecitabine). Include information about the reduced starting dose in partial DPD deficiency, followed by enhanced monitoring for toxicities.

c. As per Rule 10(1)(e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information for Fluorouracil and Capecitabine in light of the decisions of TGA, MHRA, EMA and PRAEC-DRAP.

2.2. Risk of kidney damage with oral anticoagulants

i. The Therapeutic Goods Administration (TGA) of Australia in June 2023 announced that a warning about serious kidney damage has been added to the prescribing information for all oral anticoagulants given through the oral route. Anticoagulant-related nephropathy (ARN) is a rare but serious adverse event resulting from profuse glomerular bleeding and has the potential to cause irreversible kidney damage and death. The TGA investigated the safety signal based on reports of ARN in patients taking oral anticoagulants, mainly from overseas and sought a piece of advice from the Advisory Committee on Medicines (ACM). The committee noted that this adverse event is now well documented in the medical literature with warfarin and there is growing evidence for other oral anticoagulants. The ACM supported a class-wide warning being added to the Product Information for all oral anticoagulants. The ACM does not consider a warning for parenteral anticoagulants to be needed at this stage. This is because they are mainly used in hospitals and for a shorter duration.

ii. Healthcare professionals were informed that early detection and intervention of ARN is critical to reducing permanent kidney damage and death. Although anticoagulant-related nephropathy is rare, it is likely underdiagnosed as kidney biopsy is required for a definitive diagnosis but is rarely performed in people taking anticoagulants, and patients who develop ARN have comorbidities that may explain their acute kidney injury presentation. Therefore, healthcare professionals were advised that while treating patients who are taking oral anticoagulants, talk to them about the risk of anticoagulant-related nephropathy. Close

monitoring, including renal testing, is recommended for those with excessive anticoagulation (or supratherapeutic INR for those on warfarin) and haematuria.

iii. Oral anticoagulants are widely used to prevent and treat thromboembolic conditions and include apixaban, dabigatran, rivaroxaban and warfarin etc. Anticoagulants, sometimes called blood thinners, reduce the blood's natural ability to clot.

Decision: The PRAEC decided as follows:

a. As per Rule 10(1)(h)(iv) of the Pharmacovigilance Rules, 2022 registration holders should include information about Anticoagulant-related nephropathy (ARN) and its monitoring and evaluation in the warning and precaution section and to list ARN as an adverse drug reaction of unknown frequency in the prescribing information/label for oral anticoagulants.

b. As per Rule 10(1)(e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information for oral anticoagulants in light of the decision of TGA and PRAEC-DRAP.

2.3. Moderna and Pfizer COVID-19 vaccines: Risk of heavy menstrual bleeding.

i. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) in October 2022 recommended that heavy menstrual bleeding should be added to the product information as an adverse reaction of unknown frequency for COVID-19 vaccines Moderna (elasomeran, Spikevax®), Pfizer (tozinameran, Comirnaty®) and the bivalent vaccines. Heavy menstrual bleeding may be defined as bleeding characterized by an increased volume and/or duration which interferes with the person's physical, social, emotional and quality of life. It was informed by the agency that cases of heavy menstrual bleeding were reported after the first, second and booster doses of these vaccines. The PRAC reviewed available data, including cases reported during clinical trials, cases spontaneously reported in Eudravigilance (European database) and findings from the medical literature. Most cases appeared to be non-serious and temporary in nature. The PRAC concluded that there is at least a reasonable possibility that the occurrence of heavy menstrual bleeding is causally associated with these vaccines and therefore update of the product information was recommended. It was further informed that there is no evidence to suggest the menstrual disorders experienced by some people have any impact on reproduction and fertility. Available data provide reassurance about the use of mRNA COVID-19 vaccines before and during pregnancy. A review carried out by EMA's Emergency Task Force showed that mRNA COVID-19 vaccines do not cause pregnancy complications for expectant mothers and their babies, and they are as effective at reducing the risk of hospitalisation and deaths in pregnant people as they are in non-pregnant people. The Committee reiterates that the totality of data available confirms that the benefits of these vaccines greatly outweigh the risks.

ii. Two cases of menstrual abnormality and menorrhagia (abnormally heavy bleeding at menstruation) were reported through the E-reporting system to National Pharmacovigilance Centre (NPC), DRAP. One case with Moderna (elasomeran,), and one with booster Pfizer- Comirnaty® (tozinameran) in Pakistan in November, 2021 and January 2023 were reported to NPC.

iii. Tozinameran and elasomeran are indicated for active immunization to prevent COVID-19 caused by the SARS-CoV-2 virus.

Decision: The PRAEC decided as follows:

a. As per Rule 10(1)(h)(iv) of the Pharmacovigilance Rules, 2022 registration holders should include heavy menstrual bleeding as an adverse reaction of unknown frequency in prescribing information/label of COVID-19 vaccine Pfizer (tozinameran, Comirnaty®).

b. As per Rule 10(1)(b) of the Pharmacovigilance Rules, 2022 recommended National Pharmacovigilance Centre to issue a safety alert for both the COVID-19 vaccine Pfizer (tozinameran) and Moderna (elasomeran).

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

2.4. Moderna and Pfizer COVID-19 vaccines: Risk of myocarditis and pericarditis

i. The Therapeutic Goods Administration (TGA) of Australia in October, 2022 announced that the product information for COVID-19 vaccines Moderna and Pfizer and the bivalent vaccines be updated to expand on an existing warning on myocarditis and pericarditis to include the following points: rare cases can also occur in females; cases of myocarditis and pericarditis following vaccination have rarely been associated with severe outcomes including death; and the signs and symptoms of myocarditis and pericarditis following vaccination include atypical presentations and non-specific symptoms of fatigue, nausea and vomiting, abdominal pain, dizziness or syncope, oedema and cough. The agency initially added a warning statement to the Consumer Medicine Information and Product Information for the Comirnaty Vaccine back in July, 2021.

ii. Likewise, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) in July 2021 concluded that very rare cases of myocarditis and pericarditis can occur following vaccination with the COVID-19 vaccines tozinameran (Comirnaty®) and elasomeran (Spikevax®), and recommended the listing of myocarditis and pericarditis as adverse effects in the product information for these vaccines. The review included an in-depth analysis of 145 cases of myocarditis and 138 cases of pericarditis following the use of tozinameran, and 19 cases of myocarditis and 19 cases following the use of elasomeran in the European Economic Area (EEA). The PRAC concluded that the cases primarily occurred within

14 days after vaccination, more often after the second dose and in younger adult men. Also, five death cases were reported. Based on the reviewed data, the PRAC has determined that the risk for both of these conditions is overall "very rare", meaning that up to one in 10,000 vaccinated people may be affected. Healthcare professionals were advised to counsel vaccinated individuals to seek immediate medical attention when they experience chest pain, shortness of breath, or palpitations.

iii. The Ministry of Health, Labour and Welfare of Japan (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan in July, 2021 announced that the package inserts for tozinameran and elasomeran should be revised to include the risk of myocarditis and pericarditis as adverse drug reactions. A total of 12 cases of myocarditis and three cases of pericarditis with the use of tozinameran have been reported in Japan, but a causal relationship was not established for any of the cases. One case of myocarditis with the use of elasomeran has been reported, but a causal relationship was not established.

iv. Tozinameran and elasomeran are indicated for active immunization to prevent COVID-19 caused by SARS-CoV-2 virus.

Decision: The PRAEC decided as follows:

a. **As per Rule 10(1)(h)(iv) of the Pharmacovigilance Rules, 2022 recommended that the registration holders of COVID-19 vaccines tozinameran (Comirnaty®) should update the prescribing information by including information about the occurrence and monitoring of myocarditis and pericarditis in the warning and precaution section and list myocarditis and pericarditis as a very rare adverse reaction.**

b. **As per Rule 10(1)(b) of the Pharmacovigilance Rules, 2022 recommended to the National Pharmacovigilance Centre-DRAP to issue a safety alert for both vaccines i.e. tozinameran (Comirnaty®) and elasomeran (Spikevax®).**

c. **As per Rule 10(1)(e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of (tozinameran, Comirnaty®) in light of the decisions of TGA, EMA, PMDA and PRAEC-DRAP.**

2.5. Cephalosporins: Risk of seizures

i. Health Canada in January, 2023 announced that the product safety information for cephalosporins will be updated to include the risk of seizures in all the cephalosporins. As the risk of seizures was already included for some cephalosporins, this update was applied to cephalosporins that did not include the risk. The review was triggered by a US Food and Drug Administration update to the product safety information for cefazolin to include the risk of seizures. Accordingly, the Health Canada reviewed the available information from searches of the Canada Vigilance database, international databases, as well as medical and scientific literature. Health Canada reviewed 84 cases (7 domestic and 77 international) of seizures in patients taking cephalosporins. Of the 84 cases, 13 cases (all international) were found to be probably linked to the use of cephalosporins, and 62 cases (4 domestic and 58 international) were found to be

possibly linked. Three cases (all international) were unlikely to be linked to the use of cephalosporins. Six cases (3 domestic and 3 international) could not be assessed. The review concluded that there may be a link between the use of cephalosporins and the risk of seizures and therefore the agency informed that it would work with manufacturers to update the Canadian Product Monographs for the cephalosporins that did not already include the risk.

ii. The New Zealand Medicines and Medical Devices Safety Authority (Medsafe) in its publication dated 2nd March, 2023 informed that the risk of neurotoxicity with cephalosporins was discussed at the December 2022 Medicines Adverse Reaction Committee (MARC) meeting wherein the committee recommended that all cephalosporin data sheets should include consistent messaging on the risk of neurotoxicity. Cephalosporin-induced neurotoxicity may present as a range of conditions which are mainly characterised by encephalopathy, myoclonus and/or seizures. Seizures associated with cephalosporins may present as either convulsive or non-convulsive. Symptoms of neurotoxicity have been reported to develop within several days after starting treatment and to resolve following discontinuation. In patients with renal impairment, accumulation can occur, especially when doses are not adjusted appropriately, potentially leading to toxic effects. Additional risk factors for cephalosporin-induced neurotoxicity include older age groups, underlying central nervous system (CNS) disorders and high doses of cephalosporins administered by intravenous injection.

iii. Cephalosporins are a group of prescription antibiotic medicines (cephalexin, cefazolin, cefadroxil, cefoxitin, cefuroxime, cefprozil, cefotaxime, ceftazidime, ceftriaxone, cefixime, cefepime, ceftobiprole and ceftolozane-tazobactam) and are indicated for the treatment of a wide range of bacterial infections including urinary and respiratory tract infections.

Decision: The PRAEC decided as follows:

a. As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 the registration holders of all cephalosporins should include information on the risk of seizures/ neurotoxicity in the warning and precaution section and also list in adverse drug reaction section in the prescribing information/label of all cephalosporins.

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

2.6. Third-generation aromatase inhibitors: Risk of tendon disorders.

i. Health Canada in January, 2023 announced that the product safety information for third-generation aromatase inhibitors (anastrozole, exemestane and letrozole) will be updated to include the risk of tendon disorders. The review was triggered by an update including the risks of tendonitis and tendon rupture by the EMA to letrozole product safety information. It was informed that Health Canada is working with the manufacturers of third-generation aromatase inhibitors to update the Candian Product

Monographs to include these risks. Tendon disorders include tendon inflammation (tendonitis), inflammation of the tendon sheath (tenosynovitis) and tendon tears (tendon rupture).

ii. Health Canada reviewed reports of events of tendonitis and tenosynovitis and their potential relation to tendon rupture in five randomized controlled trials (RCTs). The agency also reviewed 25 case reports (2 domestic and 23 international) of tendon rupture (10 cases) and tendonitis (15 cases), where a link between the risk of tendon rupture and tendonitis with the use of a third-generation aromatase inhibitor could not be ruled out. However, these case reports included other medications and/or conditions that could have contributed to the reported adverse events. The review concluded that there is likely a link between the use of third-generation aromatase inhibitors and the risks of tendonitis and tenosynovitis. Also, a link with tendon rupture could not be ruled out.

iii. Third-generation aromatase inhibitors (anastrozole, exemestane and letrozole) are prescription drugs authorized for the treatment of breast cancer in women who have reached menopause (post-menopausal breast cancer).

Decision: The PRAEC decided as follows:

a. As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders of third-generation aromatase inhibitors (anastrozole, exemestane and letrozole) should update their prescribing information by including information about tendon disorders (tendonitis, tendon rupture and tenosynovitis etc.) in the warning and precaution section and list these in adverse drugs reaction section.

b. As per Rules 10 (1)(e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of third-generation aromatase inhibitors (anastrozole, exemestane and letrozole) in light of the decisions of Health Canada and PRAEC-DRAP.

2.7. Terlipressin: Risks of respiratory failure, sepsis.

i. The Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom (UK) in March 2023 announced that the Pharmacovigilance Expert Advisory Group of the UK's Commission on Human Medicines agreed with the recommendations made as a result of EMA's review which was triggered by the CONFIRM trial findings that new measures were required to reduce the risk of respiratory failure and sepsis when terlipressin is used in patients with type 1 hepatorenal syndrome. The clinical trial found that in patients with type 1 hepatorenal syndrome, terlipressin may cause serious or fatal respiratory failure at a frequency higher than previously known and that terlipressin increases the risk of sepsis and septic shock. Healthcare professionals were advised to consider the individual benefits and risks for patients with type 1 hepatorenal syndrome when initiating terlipressin treatment, especially for those with severe renal or hepatic impairment and monitor all patients closely during terlipressin treatment. The advice is not relevant to the use of terlipressin for bleeding oesophageal varices.

ii. Previously, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in September 2022 recommended new measures to reduce the risk of respiratory failure and sepsis when using terlipressin in people with type 1 hepatorenal syndrome (HRS-1), which is a serious kidney problem in people with advanced liver disease. The recommendations follow the PRAC's review of available data, including results from the CONFIRM clinical trial that included patients with HRS-1. Results of the trial suggested that patients who were treated with terlipressin were more likely to experience and die from respiratory disorders within 90 days after the first dose than those who were given a placebo. Although respiratory failure is a known adverse effect of terlipressin, the frequency of respiratory failure seen in the study was higher (11%) than previously reported in the product information. In addition, the study reported sepsis in 7% of patients in the terlipressin arm compared with none in the placebo group. The new measures include adding a warning to avoid terlipressin in patients with advanced acute-on-chronic liver disease or advanced kidney failure, to the product information. Patients with breathing problems should receive treatment to manage their condition before starting terlipressin. During and after treatment, patients should be monitored for signs and symptoms of respiratory failure and infection. In addition, healthcare professionals can consider giving terlipressin-containing medicines as a continuous infusion (drip) into the vein as an alternative to giving it by bolus injection (full dose injected in one go) as this may reduce the risk of severe side effects. The PRAC recommendations were sent to the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) which endorsed them and adopted its position on 10 November 2022. Furthermore, the label of Terlipressin (**TERLIVAZ**)- US-FDA also contains a Boxed Warning about respiratory failure.

iii. Terlipressin is a synthetic pituitary hormone indicated for the treatment of bleeding from dilated veins in the food pipe leading to the stomach (bleeding oesophageal varices) and for emergency treatment of type 1 hepatorenal syndrome (rapidly progressive renal failure in patients with liver cirrhosis (scarring of the liver) and ascites (fluid accumulation in the abdomen)).

Decision: The PRAEC decided as follows:

a. As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 registration holders should include information about strict monitoring of respiratory failure and sepsis when using terlipressin in people with type 1 hepatorenal syndrome (HRS-1) in the warning and precaution section. Adding a warning to avoid terlipressin in patients with advanced acute-on-chronic liver disease or advanced kidney failure and information that patients with breathing problems should receive treatment to manage their condition before starting terlipressin-containing medicines in the prescribing information/ label of terlipressin when used in people with type 1 hepatorenal syndrome (HRS-1).

b. Registration holders should create a boxed warning in the prescribing information for terlipressin medicines when used in people with type 1 hepatorenal syndrome (HRS-1) as per the below format:

WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

Terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or with ACLF Grade 3 are at increased risk. Assess oxygenation saturation (e.g., SpO2) before initiating terlipressin.

Do not initiate terlipressin in patient experiencing hypoxia (e.g,, SpO2 < 90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue Terlipressin if SpO2 decreases below 90%.

c. As per Rule 10(1)(e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of terlipressin when used in people with type 1 hepatorenal syndrome (HRS-1) in light of the decision of MHRA, EMA and PRAEC-DRAP.

2.8. Gemifloxacin: Risk of Genotoxicity

i. The Egyptian Pharmacovigilance Center (EPVC), Egyptian Drug Authority (EDA) in January, 2023 announced that the registration of products containing gemifloxacin is cancelled. The technical committee of the EDA found the risk-benefit balance of gemifloxacin no more favourable due to the potential genotoxicity of gemifloxacin and the availability of safer quinolone products in the Egyptian market. The committee decided to cease the marketing of products.

ii. Previously, the European Medicine Agency in 2009, decided to withdraw an application for a centralized marketing authorization for the medicine Factive® (gemifloxacin), 320 mg film-coated tablets. On 17 June 2009, Menarini International Operations Luxembourg S.A. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wished to withdraw its application for a marketing authorisation for Factive. The medicine was expected to be used for the treatment of bacterial infections causing mild to moderate community-acquired pneumonia and acute exacerbation of chronic bronchitis. At the time of the withdrawal, it was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP). In its official letter, the company stated that the withdrawal of the application was based on the CHMP's view that the data provided did not allow the Committee to conclude on a positive benefit-risk balance.

iii. The CHMP was concerned that Factive® (gemifloxacin), maybe more genotoxic (harmful to the DNA, the genetic material in cells) and that it may therefore cause more damage to the DNA than other fluoroquinolones. The Committee was also concerned there was not enough evidence of the effectiveness of Factive in patients with moderate community-acquired pneumonia when given as a five-day treatment. The seven-day treatment was not considered acceptable because of the risk of side effects. The Committee also noted that the information presented did not support the use of Factive for chronic bronchitis because no studies were carried out to investigate whether

Factive was better than other treatments for this type of infection and because there were problems with the studies that were performed. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Factive in the treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis caused by bacterial infection did not outweigh its risks.

iv. Likewise, as per the publicly available information on the US-FDA website, the Factive (Gemifloxacin Mesylate) and its generic are discontinued in the United States.

v. Gemifloxacin is a quinolone antibiotic and is indicated for the treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis caused by bacterial infection.

Decision: **The PRAEC decided to defer the case and advised NPC to present the regulatory status of Gemifloxacin in other agencies including reference regulatory authorities and prepare a proposal in consultation with the Divison of PE&R, keeping in view the availability of other safer quinolone antibiotic.**

2.9. Codeine with ibuprofen: Risks of serious renal and gastrointestinal harms.

i. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in September 2022 recommended a change to the product information for codeine with ibuprofen combination medicines to include a warning of serious harms, including death, particularly when taken for prolonged periods at higher than recommended doses.

ii. The PRAC reviewed several cases of renal, gastrointestinal and metabolic toxicities that have been reported in association with cases of abuse of and dependence from codeine with ibuprofen combinations, some of which have been fatal. The PRAC found that, when taken at higher than recommended doses or for a prolonged period of time, codeine with ibuprofen can cause damage to the kidneys, preventing them from removing acids properly from the blood into the urine (renal tubular acidosis). Kidney malfunction can also cause hypokalaemia, which in turn may cause symptoms such as muscle weakness and light-headedness. Therefore, renal tubular acidosis and hypokalaemia will be added to the product information as new adverse effects. The PRAC noted that medicines containing a combination of codeine and ibuprofen are authorised at the national level and in some countries these medicines are available without medical prescription. The PRAC considered that prescription-only medicine status would be the most effective risk minimisation measure to mitigate the harm associated with abuse and dependence of these products.

iii. Codeine with ibuprofen is a combination of opioid (codeine) and anti-inflammatory (ibuprofen), which is used to treat pain. Repeated use of codeine with ibuprofen may lead to dependence and abuse due to the codeine component.

Decision: The PRAEC decided as follows:

a. **As per Rule 10(1)(h)(iv) of Pharmacovigilance Rules, 2022 that registration holders of Codeine with Ibuprofen combination should include information about serious harms (renal, gastrointestinal and metabolic toxicities) including death, particularly when taken for prolonged periods at higher than recommended doses in the warning and precaution section, and to add renal tubular acidosis and hypokalaemia as adverse drug reactions in the prescribing information/ label of codeine with ibuprofen combination.**

b. **As per Rule 10(1)(e) of the Pharmacovigilance Rules, 2022 recommended the Registration Board to update the prescribing information of drugs containing Codeine with Ibuprofen in light of the decision of EMA and PRAEC-DRAP.**

3. ADDITIONAL AGENDA.

3.1. Co-opt a member of PRAEC.

PRAEC deliberated that a few cases related to drug sales and usage at the point of sale are often discussed during the meeting. The committee, therefore, decided to co-opt Sardar Shabbir Ahmed, Secretary, Quality Control Board/Focal Person for Pharmacovigilance, Islamabad as an expert member on the sale of drugs for Pharmacovigilance Risk Assessment Expert Committee (PRAEC) as per Rule 9 (5) of Pharmacovigilance Rules, 2022

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