MINUTES OF 2ND MEETING OF PHARMACOVIGILANCE RISK ASSESSMENT EXPERT COMMITTEE

The National Pharmacovigilance Centre, Division of Pharmacy Services, Drug Regulatory Authority of Pakistan

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DRUG REGULATORY AUTHORITY OF PAKISTAN

Telecom Foundation Complex, 7th Mauve Area, G-9/4, Islamabad

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Minutes of the 2nd meeting of the Pharmacovigilance Risk Assessment Expert Committee.

The 2nd 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 7th of March, 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, 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.	Secretary
4	Prof. Dr Madeeha Malik, Professor, Pharmacy Practice, Hamdard Institute of Pharmaceutical Sciences, Hamdard University, Islamabad.	Member
5	Mr Shoukat Sahad, Chief Pharmacist, Rehman Medical Institute (RMI), Peshawar.	Member
6	Mr Syed Shamim Raza, Director, Services Line and Chief, Pharmacy Services, Agha Khan University Hospital, Karachi.	Member
7	Dr Khalid Mehmood, Associate Prof./Head of Pharmacy, Department of Pharmacy, Abbottabad University of Science & Technology, Abbottabad.	Member
8	Dr Maryyum Sarfraz, Associate Professor, Health Services Academy, Islamabad.	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 1st meeting of PRAEC.

The 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held on the 12th of October, 2022. The minutes of the meeting were prepared and shared with expert members through email and were finalized in light of the emails of members on 24-10-2022. Accordingly, as per minutes of the 1st meeting of PRAEC, the safety alerts were issued and decisions were communicated to the concerned Divisions of the DRAP. In this regard, the minutes of the 1st meeting were placed before the PRAEC for confirmation as per the Standard Operating Procedure vide document no PHSR/SOP/PC/018.

Decision:

All the members confirmed the minutes of 1st meeting of PRAEC held on the 12th October, 2022.

1.2. Declaration of the Non-existence of Conflict of Interest

The Drug Regulatory Authority of Pakistan (DRAP) has developed a Code of Conduct and Non-Conflict of Interest Document having document No ADMN/GL/CC/001, dated 15-06-2022. As per section 12.5.1 of this code, members of Boards and Committees of the DRAP are required to submit an affidavit for the Non-existence of Professional and/or Financial Conflict of Interest on the prescribed format to the DRAP. Therefore, members/experts of the Pharmacovigilance Risk Assessment Expert Committee of the DRAP have to submit an affidavit for the Non-existence of Professional and Financial Conflict of Interest on the prescribed format **(Annex-A)** of the aforementioned code to the DRAP in order to ensure that there is no influence of any sort on the decisions of Pharmacovigilance Risk Assessment Expert Committee.

The case was discussed in the first meeting of PRAEC held on 12th of October, 2022, which decided as under:

> *"It was decided that a soft copy of the Proforma D of the Code of Conduct and Non-Conflict of Interest Document of the DRAP will be emailed to the members for submission of the affidavit as per practice on stamp paper."*

The case was again discussed in the second meeting of PRAEC.

Decision:

The PRAEC decided that all the members (experts) shall submit the affidavit for the non-existence of professional and financial conflict of interest on plain paper as per Annex-A to the National Pharmacovigilance Centre, DRAP.

1.3. Appointment of Qualified Person for Pharmacovigilance by registration holders.

Rule 11 (2) of the Pharmacovigilance Rules, 2022 obligates the registration holders to appoint a Qualified Person for Pharmacovigilance (QPPV), which is reproduced as under:

"The registration holder shall appoint a qualified person for pharmacovigilance (QPPV), having such experience and qualification as defined by DRAP, who shall be responsible for pharmacovigilance system and shall reside and operate in the country, and shall also be responsible for establishment and maintenance of the pharmacovigilance system. In the case of a multinational registration holder, the nomination of a local safety officer (LSO) will also be accepted, who shall reside and operate in the country. The registration holder shall submit the name and contact details of the qualified person to NPC."

Accordingly, further guidelines in respect of QPPV/LSO were provided to registration holders in Module 1 of the Guidelines on Good Pharmacovigilance Practices for Registration Holders. The Module also defines the list of documents which are to be submitted by registration holders along with the nomination of QPPV/LSO. Furthermore, the roles and qualifications of the QPPV/LSO have also been defined. However, very few registration holders have submitted the nomination of their QPPV/LSO to National Pharmacovigilance Centre.

In order to ensure the nomination of QPPV/LSO by each registration holder of therapeutic goods, there is a need to link the renewal of the licence of registration holders with the nomination of QPPV/LSO. In this regard, the Drugs Licensing, Health & OTC and Medical Devices and Medicated Cosmetics Divisions of the DRAP may be requested to get the nomination of QPPV/LSO (along with necessary documents) at the time of renewal of the license of therapeutic goods. Accordingly, the renewal license should be issued to only those registration holders who have submitted their nomination of QPPV/LSO along with the necessary documentation.

The case was submitted to PRAC in its 2nd meeting for its deliberation.

Decision:

The PRAEC deliberated the matter in light of relevant provisions of law and decided that National Pharmacovigilance Centre should hold a consultative meeting with other Divisions of

DRAP to discuss the possibility of linking the renewal of the license/registration with the submission of the nomination of QPPV/LSO by registration holders. In this regard, an implementation strategy/plan may be developed and presented before the PRAEC in its next meeting for its consideration.

2. DOMESTIC SIGNALS

2.1. Hypersensitivity Reactions with Pegaspargase (Peg L Asparaginase).

Introduction

Pegaspargase is a conjugate of monomethoxypolyethylene glycol (mPEG) and L-asparaginase (L-asparagine amidohydrolase), an asparagine specific enzyme. L-asparaginase is a tetrameric enzyme that is produced endogenously by E. coli and consists of identical 34.5 kDa subunits. L-asparaginase is an enzyme that catalyzes the conversion of the amino acid L-asparagine into aspartic acid and ammonia. The pharmacological effect of Pegaspargase is thought to be based on the killing of leukemic cells due to the depletion of plasma asparagine. Leukemic cells with low expression of asparagine synthetase have a reduced ability to synthesize asparagine, and therefore depend on an exogenous source of asparagine for survival. Normal cells, in contrast, are capable of synthesising L-asparagine and are less affected by its rapid depletion during treatment with the enzyme L-asparaginase. The PEGylation does not change the enzymatic properties of L-asparaginase, but it influences the pharmacokinetics and immunogenicity of the enzyme.

Pegaspargase is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with ALL and hypersensitivity to native forms of L-asparaginase. The recommended dose of Pegaspargase for patients up to and including 21 years of age is 2,500 International Units/m2 intramuscularly or intravenously no more frequently than every 14 days. The recommended dose of Pegaspargase for adult patients more than 21 years of age is 2,000 International Units/m2 intramuscularly or intravenously no more frequently than every 14 days. Pegaspargase can be given by intramuscular (IM) injection or intravenous (IV) infusion. For smaller volumes, the preferred route of administration is intramuscular. When Pegaspargase is given by intramuscular injection the volume injected at one site should not exceed 2 ml in children and adolescents, and 3 ml in adults. If a higher volume is given, the dose should be divided and given at several injection sites. Intravenous infusion of Pegaspargase is usually

given over a period of 1 to 2 hours in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution. The diluted solution can be given together with an already-running infusion of either sodium chloride 9 mg/ml or 5% glucose. Do not infuse other medicinal products through the same intravenous line during the administration of Pegaspargase.)

Hypersensitivity reactions are exaggerated or inappropriate immunologic responses occurring in response to an antigen or allergen. Type I, II and III hypersensitivity reactions are known as immediate hypersensitivity reactions because they occur within 24 hours of exposure to the antigen or allergen. Immediate hypersensitivity reactions are predominantly mediated by IgE, IgM, and IgG antibodies. The fourth type is considered a delayed hypersensitivity reaction because it usually occurs more than 12 hours after exposure to the allergen, with a maximal reaction time between 48 and 72 hours. A Type IV hypersensitivity reaction is mediated by T cells that provoke an inflammatory reaction against exogenous or endogenous antigens. In certain situations, other cells, such as monocytes, eosinophils, and neutrophils, can be involved. Previously, in 1963, Gell and Coombs created the foundation for classifying hypersensitivity reactions by dividing them into four distinct groups according to mechanisms of tissue injury: type I (immediate or immunoglobulin E [IgE] mediated), type II (cytotoxic or IgG/ IgM mediated), type III (immune complex-mediated), and type IV (delayed-type or T-cell mediated).

Drug-induced hypersensitivity reactions represent a major concern for clinicians, patients, regulators and drug developers. Severe hypersensitivity is associated with high morbidity and mortality, it cannot be predicted from the known pharmacology of the drug and it is usually detected post-marketing when a large number of patients have been exposed to a particular drug. Hypersensitivity reactions are commonly associated with the use of certain cancer chemotherapy drugs, including platinums, taxanes, asparaginase, procarbazine, and epipodophyllotoxins. Asparaginase has a high rate of hypersensitivity reactions that are likely IgE mediated or related to complement activation. Skin testing has been recommended but has not been validated for asparaginase.

Reports & Background

The National Pharmacovigilance Centre (NPC) received six cases of hypersensitivity reactions from Indus hospital Karachi with Pegaspargase (Peg L Asparaginase) with different batches

having the same importer i.e. M/S Lab Diagnostic System and same manufacture i.e Jiangsu Hengrui Medicine Co Ltd, China. The drug was prescribed for Acute Lymphoid Leukemia/ Leukemia with a dose of 2500 IU/m2 in children. The events of hypersensitivity reactions including swelling of lips, nausea, rash, vomiting, swelling of the tongue, itching all over the body, shivering, red eyes and abdominal pain were noted in the six cases after administration of Pegaspargase (Peg L Asparaginase) 3750IU. The time to onset of reactions was one day. The Pegaspargase was withdrawn in all cases except one case where the status is unknown and the patients were recovered. The causality assessment of all six cases was performed by the Causality Assessment Group of the National Pharmacovigilance Centre (NPC) and classified all six cases to have a possible relationship with drug intake.

Assessment at National Centre.

The events in the six cases under consideration were reported with the suspected drug Pegaspargase (Peg L Asparaginase) having a strength of 3750IU. The drug labels/SmPCs published by the US FDA and MHRA-UK were searched for the reported events. Reported events of hypersensitivity reactions including related events such as swelling of lips, angioedema, rash etc were already listed in the warning and precautions and adverse drug reactions section in the label/SmPC of the United Kingdom and US-FDA.

As per MHRA and FDA label/ SmPC, hypersensitivity reactions to Pegaspargase, including life-threatening anaphylaxis, can occur during therapy, including in patients with known hypersensitivity to *E. coli*-derived asparaginase formulations. Other hypersensitivity reactions can include angioedema, lip swelling, eye-swelling, erythema, decreased blood pressure, bronchospasm, dyspnoea, pruritus and rash. Premedication of patients 30-60 minutes prior to administration of pegaspargase was advised. As a routine precautionary measure, it was also advised that the patient should be monitored for an hour after administration; resuscitation equipment and other appropriate means for the treatment of anaphylaxis should be available (epinephrine, oxygen, intravenous steroids, etc.). Pegaspargase should be discontinued in patients with serious hypersensitivity reactions. Monitoring of patients was also advised, and modification of treatment was recommended as per following schedule: reducing the infusion rate by 50% in case of Grade 1 hypersensitivity reaction; interrupting the infusion, treating the symptoms, when symptoms resolved, resuming the infusion and reducing the infusion rate by 50% in case of Grade

2 hypersensitivity reaction; and for Grade 3 to 4 hypersensitivity reactions permanent discontinuation of pegaspargase was advised.

Furthermore, there was significant disproportionality in the global database for ADR combination (hypersensitivity-Pegaspargase) with positive IC025 value along with ROR and PRR value > 1 showing potential association.

Likewise, there are also published research articles such as children's oncology group (COG) clinical trials and a retrospective chart review study on pegaspargase administration at Children's Healthcare of Atlanta. The COG trial compared severe Pegaspargase hypersensitivity reaction rates (grade ≥3) with intravenous infusion vs. intramuscular injection. Likewise, a retrospective chart review study assessed the development of hypersensitivity reactions in a cohort that included 277 recipients who were administered at least one dose of pegaspargase during the 3 years' review periods.

Accordingly, the signal was validated in light of the evaluation of reports (reasonable time to onset), statistical analysis in VigiLyze, literature search and available label/ SmPC of other agencies. Therefore, the case was submitted before the PRAEC in light of the recommendation of the assessors.

DISCUSSION:

PRAEC discussed the matter in detail as per the following details:

- Pre-medication/chemo protocol is mandatory for all chemotherapy drugs and is part of standard treatment guidelines. Furthermore, the Committee also considered that the rate of infusion/administration could have caused infusion-related hypersensitivity reactions, therefore, there might be an error in the procedures of the Indus hospital Karachi by mishandling the drugs due to a lack of training.
- The committee enquired whether the cause of the ADRs could be due to the quality problem of this specific brand. It was informed to the committee that quality testing was not carried out as the reactions were reported with different batches of pegaspargase and the reaction of hypersensitivity reactions with Pegaspargase is already listed in the MHRA/FDA label.
- The committee discussed the possibility to conduct a retrospective or prospective study to search medication records of patients to evaluate the actual numbers of cases that could have happened in all the hospitals where the pegaspargase is/was being used. It was also discussed that there are chances that the hospitals where the drug was used might not have maintained reported ADR records. Moreover, the practice-related problem of the hospital

could not be identified due to the lack of complete patient records. But the prospective study can be done if required.

- The local label/prescribing information of Pegaspargase was presented before the PRAEC, wherein it was noted that the prescribing information does not contain detailed information about the hypersensitivity reaction (HSR), dose modification after the occurrence of HSR and guidance for healthcare professionals for monitoring, preparation, administration and availability of resuscitation equipment and other appropriate means for the treatment of anaphylaxis/hypersensitivity reactions such as epinephrine, oxygen, intravenous steroids at the administration sites.
- The importer of the drug i.e. M/S Lab Diagnostic Pakistan was allowed to present their comments before the Committee on the issue. The representatives of the firm namely Mst Sabiha Khan and Mst Mehak Maqsood informed that the drug is being used in 20 hospitals having Oncology treatment facilities across Pakistan. The representatives also apprised the committee that two more hypersensitivity reactions of grade II were reported directly to the company by Doctor's Hospital, Lahore. The representative informed that Indus Hospital Karachi is the major user of Pegaspargase as it consumed one-third of the total doses used monthly in Pakistan. However, the six reported ADRs only account for 0.01% of the total doses consumed in the last six months.
- The company also informed that had a plan to conduct educational training for healthcare professionals in all the hospitals where the drug is used, but could not materialise due to some reasons. It was informed that the firm had displayed dose adjustment charts in different hospitals after the occurrence of HSR reactions as per their grade.
- Going into the further discussion to conclude the discussion, the Committee noted that there could be a reason of lack training at the treatment sites of hospitals regarding the Pegaspargase chemotherapy protocol, which might have caused the reaction in only two of the twenty hospitals. In this regard, an issuance of advisory to all hospitals where Pegaspargase would reduce the chances of HSRs due to mishandling. Furthermore, the issuance of the advisory will further enhance the reporting of ADRs to the national centre in general with all drugs.
- Likewise, the committee discussed the update of the prescribing information/safety specification of Pegaspargase to include information about hypersensitivity reactions and its monitoring in the warning and precaution; and dose modification after the occurrence of HSRs along with educational training for healthcare professionals and concluded that it is need of the hour and it must be done at the earliest along with the establishment of proper pharmacovigilance system by the importer.

Decision:

A. The PRAEC after detailed deliberation and discussion decided to recommend to the Registration Board of the DRAP as per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 as follows:

1. ***To direct registration holders to change/update the prescribing information/safety specification of Pegaspargase by including the following information:***

    a. ***Information related to hypersensitivity reactions and its monitoring in the warning and precaution sections; and***

    b. ***Information on treatment modification as per the grade of hypersensitivity reactions in dosage and administration sections.***

2. ***To direct registration holders to introduce an educational training programme for healthcare professionals on proper preparation, administration and monitoring of Pegaspargase and to ensure that resuscitation equipment and other appropriate means for the treatment of anaphylaxis/hypersensitivity reactions such as epinephrine, oxygen, intravenous steroids, etc. are available at the administrative sites.***

3. ***The importer should establish an active pharmacovigilance system by appointing a Qualified Person for Pharmacovigilance (QPPV) within 15 days and regularly submit the data of collected ADRs to the National Pharmacovigilance Centre as per Pharmacovigilance Rules, 2022.***

B. ***The PRAEC also decided to recommend to National Pharmacovigilance Centre (NPC), DRAP as per Rule 10 (1) (b) to issue an advisory to all hospitals where Pegaspargas is distributed in Pakistan to strictly follow standard chemotherapy protocol for preparation, administration and monitoring of Pegaspargas.***

3. RELIANCE OF INTERNATIONAL SAFETY DECISION.

3.1. Buprenorphine: Risk of dental problems

The United States Food and Drug Administration (US-FDA) on 12th of January, 2022 through a drug safety communication warned that dental problems have been reported with medicines containing buprenorphine that are dissolved in the mouth. Dental problems, including tooth decay, cavities, oral infections, and loss of teeth have been reported, even in patients with no prior history of dental issues. The buprenorphine medicines that are associated with dental problems are tablets and films that are dissolved under the tongue or placed against the inside of the cheek. There are also buprenorphine products for pain and opioid use disorder (OUD) delivered by other routes such as a skin patch and injection, but FDA has not identified a concern for dental health related to these other forms.

Patients were advised to continue taking buprenorphine medicine as prescribed and not to stop it suddenly as it could lead to serious consequences including withdrawal symptoms. Patients were also advised to take extra steps to reduce the risk of serious dental problems such as rinsing their mouth with water and waiting at least 1 hour before brushing their teeth after buprenorphine medicines are dissolved to avoid damage to their teeth and to give the mouth a chance to return to its natural state.

Healthcare professionals were advised to be aware that the benefits of buprenorphine medicines clearly outweigh the risks in treating OUD patients and should ask patients about oral health history before prescribing treatment with the transmucosal buprenorphine medicines. Healthcare professionals should also council patients about the potential for dental problems and the importance of taking extra steps after the medicine has completely dissolved, including to gently rinse their teeth and gums with water and then swallow and to wait at least 1 hour before brushing their teeth.

Buprenorphine is an opioid used to treat opioid use disorder (misuse of prescribed opioid medications) and pain. The comprehensive approach of buprenorphine combined with counselling and other behavioural therapies is often one of the most effective ways to treat OUD. At proper doses, buprenorphine also decreases the pleasurable effects of other opioids, making misuse of them less appealing.

Decision:

- ***The PRAEC decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 to update the prescribing information/safety specification of buprenorphine medicines that are dissolved in the mouth by including information related to the risk of dental issues, pre-prescribing assessment of patients and guidelines of taking extra steps after use in the warning and precaution section.***
- ***To recommend Registration Board to update the prescribing information of buprenorphine-containing medicines that are orally dissolved in light of the PRAEC decision and as per the US-FDA label.***

3.2. Benzodiazepines: Potential Risk of Abuse, Dependence and Withdrawal.

The Medsafe of Newzealand in June 2022 reminded prescribers about the update to the product information for benzodiazepines regarding the potential risks of abuse, dependence and

withdrawal, even when taken at recommended dosages. As per information, the dispensing data of New Zealand showed that diazepam and lorazepam are the most dispensed benzodiazepines. The total amount of these medicines that were dispensed for all indications increased in the period between 2016 and 2020 which suggested frequent and/or long-term use. As per data shared, between August 1969 and March 2022, the Centre for Adverse Reactions Monitoring (CARM) received 23 case reports of withdrawal and/or dependence with the use of benzodiazepines. Clonazepam (nine cases) was the most frequently reported benzodiazepine, followed by lorazepam (five), diazepam (three) and triazolam (three). Therefore, Medsafe advised healthcare professionals to counsel patients about the risks of benzodiazepines when initiating treatment, regularly review the ongoing need for treatment, and gradually taper benzodiazepines following continuous or high-dose use to reduce the risk of withdrawal reactions.

Medsafe advised healthcare professionals to assess each patient's risk for abuse, misuse, and addiction before prescribing and throughout treatment. Likewise, caution should be taken when prescribing benzodiazepines to patients with a history of alcohol or drug abuse. When prescribing a benzodiazepine for anxiety or insomnia, it must be ensured that the patient understands that these medicines are intended for short-term use (2-4 weeks). Ongoing use of benzodiazepines may lead to dependence that increases with the dose and duration of treatment and in patients with a history of alcohol or drug abuse or a marked personality disorder. Therefore, healthcare professionals should regularly review the ongoing need for treatment, particularly if the patient is at high risk of dependence. Abrupt discontinuation or rapid dosage reduction of benzodiazepines after continued use may lead to withdrawal reactions. The likelihood and degree of severity of withdrawal depend on the duration of treatment, dose and degree of dependency. Sudden cessation of benzodiazepines that have been used continually and/or at high doses is associated with serious withdrawal reactions, such as convulsions, delirium or psychosis. Therefore, healthcare professionals should inform patients of these risks and advise them to consult their doctor before decreasing the dose or abruptly stopping the medicine. Patients should also be advised that stopping treatment requires an individualised tapering schedule which is supervised by their doctor.

Back in September 2020 and also through Podcast in January 2022, the United States Food and Drug Administration (US-FDA) through a Drug Safety Communication informed that the agency is requiring Boxed warnings of all benzodiazepines drugs to include information about the risk of abuse, misuse, addiction, physical dependence and withdrawal reactions. Abuse and misuse can result in overdose or death, especially when benzodiazepines are combined with other medicines, such as opioid pain relievers, alcohol, or illicit drugs. Physical dependence can occur when benzodiazepines are taken steadily for several days to weeks, even as prescribed. Stopping them abruptly or reducing the dosage too quickly can result in withdrawal reactions, including seizures, which can be life-threatening. The boxed warning also states that concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Therefore, these medicines may be reserved concomitant prescribing for use in patients for whom alternative treatment options are inadequate.

Healthcare professionals prescribing a benzodiazepine were advised to consider the patient's condition, any concomitant medicines and assess the risk of abuse, misuse and addiction. Also, healthcare professionals should limit the dosage and duration of the prescribed benzodiazepine to the minimum needed to achieve the desired clinical effect. Upon discontinuation, dosage should be reduced gradually to reduce the risk of acute withdrawal reactions. Precautions should be taken when benzodiazepines are used in combination with opioid drugs.

Benzodiazepines are indicated to treat generalized anxiety disorders, insomnia, seizures, social phobia and panic disorders.

Decision:

A. The PRAEC decided as per Rule 10 (1) (h) (iv) & (vi) of Pharmacovigilance Rules, 2022 as follows:

I. Registration holders of all benzodiazepines should update the prescribing information/safety specification by including information related to abuse, misuse, addiction and withdrawal in the warning and precaution section;

II. Registration holders should create the boxed warning in the prescribing information/safety specification as per the below format;

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS.

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.
- The use of benzodiazepines, including **Drug X** exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing **Drug X** and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.
- Abrupt discontinuation or rapid dosage reduction of **Drug X** after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue **Drug X**, **or** reduce the dosage.

III. Registration holders should also include information related to abuse, misuse, addiction and withdrawal of benzodiazepine in their educational training and promotional material for healthcare professionals.

B. To recommend Registration Board to update the prescribing information of all benzodiazepine-containing medicines as per the decision of PRAEC and as per US-FDA and MedSafe, Newzealand label/prescribing information.

C. Keeping in view the sale of benzodiazepine without a prescription (if any) at medical stores/pharmacies across Pakistan, that may further enhance the patient's risk of abuse, misuse and addiction and illicit use. The PRAC decided to request the QA/LT Division of the DRAP to further coordinate with provincial drug control administrations including the drug control administration of Azad Jammu and Kashmir, Gilgit Baltistan and Islamabad to ensure strict control on the over-the-counter sale of benzodiazepine by medical stores/pharmacies and maintenance of sale records of all benzodiazepine sold through prescription.

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

The Therapeutic Goods Administration (TGA) of Australia in September 2022 announced that the product information for fluorouracil and its prodrugs capecitabine and flucytosine are to be updated to include a new warning about the potential for severe and potentially life-threatening toxicity in patients with a partial di-hydro pyrimidine dehydrogenase (DPD) deficiency. The product information for fluorouracil, capecitabine and flucytosine already includes a

contraindication for patients with known complete DPD deficiency. A review of all adverse event reports submitted to the TGA for fluorouracil, capecitabine and flucytosine up to 20 July 2022 found 11 cases (of which six cases reported a fatal outcome) and the reporter noted adverse events were possibly or likely due to DPD deficiency. In most of these cases, DPD deficiency was not tested for or confirmed in the affected patients.

Healthcare professionals were advised to consider laboratory testing for total or partial DPD deficiency before therapy is initiated or when evaluating patients experiencing related toxicities and to reduce the starting dose when partial DPD deficiency is detected.

Similarly, the Medicine and Health Product Agency (MHRA) in October 2020 had announced that the product information (SmPC and Patient Information Leaflets (PIL)) for 5-fluorouracil, capecitabine and tegafur will be updated to include information on the importance of testing for DPD deficiency before initiation of the treatment. The MHRA referred to the European safety review, wherein it was recommended that despite uncertainties in the optimal pre-treatment testing methodologies, all patients should undergo testing for DPD deficiency before the initiation of these treatments. Up to 17 June 2020, a total of 30 reports associated with a fatal outcome that describes a known or suspected DPD deficiency with fluorouracil and capecitabine were received. These include reports of testing and confirmation of DPD deficiency after patients were treated with capecitabine and developed severe and fatal toxicity. Fluorouracil is also available in topical formulations, but due to very low systemic absorption via this route, DPD testing is not required prior to initiation.

Healthcare professionals were advised to test all patients for DPD deficiency before initiation of treatment. Patients with known complete DPD deficiency should not be treated with these medicines. For patients with partial DPD deficiency, a reduced starting dose should be considered. All patients should be monitored for toxicity particularly during the first cycle of treatment or after a dose increase.

Previously in March 2020, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recommended that patients should be tested for the lack of dihydropyrimidine dehydrogenase (DPD), an enzyme needed to break down fluorouracil, before cancer treatment with fluorouracil and prodrugs (capecitabine and tegafur) via injection

or infusion. No pre-treatment testing is needed for topical treatment with fluorouracil. Lack of DPD enzyme causes fluorouracil to build up in the blood, which may lead to severe and life-threatening adverse drug reactions such as neutropenia, neurotoxicity, severe diarrhoea and stomatitis. It was advised that the patients with a known complete DPD deficiency must not be given fluorouracil, capecitabine or tegafur. For patients with a partial DPD deficiency, a reduced starting dose of these medicines should be considered.

Fluorouracil is indicated alone or in combination with other medicines to treat various cancers such as malignant tumours, particularly of the breast, colon or rectum. Also, it is applied to the skin for actinic keratosis and dermal warts. Capecitabine is indicated for the treatment of certain types of colon, colorectal, oesophagogastric and breast cancer. Flucytosine is indicated for the treatment of generalised candidiasis, cryptococcosis and chromoblastomycosis.

Decision:

The PRAEC decided to Co-opt experts of 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 from the following hospitals:

a. ***Agha Khan University Hospital, Karachi Or Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore;***
b. ***From any of the tertiary care public sector hospitals of Pakistan; and***
c. ***Pakistan Atomic Energy hospitals in Pakistan.***

3.4. Janus Kinase (JAK) Inhibitors: Risk of serious heart-related events, blood clots, cancer and death.

Health Canada in September 2022 announced that the product safety information for Janus kinase (JAK) inhibitors (including tofacitinib (Xeljanz®), baricitinib (Olumiant®), upadacitinib (Rinvoq®), abrocitinib (Cibinqo®), *ruxolitinib* (Jakavi®) and fedratinib (Inrebic®)) have been or will be updated to include the risk of serious heart-related problems, blood clots, cancer and death. Health Canada reviewed the final findings from the clinical research study from 2019 which linked tofacitinib to higher risks of serious heart-related problems, cancer and death, and confirmed the initial findings of an increased risk of blood clots. Health Canada also reviewed the interim findings from a 2021 observational study with baricitinib (Olumiant®), which showed increased rates of serious heart-related problems and

blood clots with its use. Given the similar mechanisms of action and indications, Health Canada's review concluded that a drug class effect for the risks of serious heart-related problems, blood clots, cancer and death cannot be excluded with JAK inhibitors used for the treatment of chronic inflammatory diseases, including upadacitinib, abrocitinib, ruxolitinib and fedratinib in addition to tofacitinib and baricitinib.

Back in October, 2021, the Medicine and Health Product Regulatory Agency (MHRA) of the United Kingdom announced that the product information for tofacitinib will be updated with the information that tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (e.g., diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable alternative treatments. The MHRA reviewed the results of a clinical safety trial (ORAL Surveillance) to evaluate the safety of tofacitinib compared with TNF blockers and identified these risk factors. In 2021, final results from this study showed tofacitinib to be associated with an increased incidence of non-fatal myocardial infarction and malignancies, particularly lung cancer and lymphoma.

Likewise**,** the Ministry of Health Labour and Welfare (MHLW) and Pharmaceutical and Medical Device Agency (PMDA) of Japan had also in October 2021 announced that the package inserts for tofacitinib should be revised to include the risk of cardiovascular events, such as myocardial infarction. The MHLW and the PMDA also reviewed the results of a clinical safety trial to evaluate the safety of tofacitinib compared with TNF blockers and identified.

Similarly, the United States Food and Drug Administration (US-FDA) on 1st September, 2021 through a Drug Safety Communication announced that based on a review of a large randomized safety clinical trial, the agency concluded that there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with arthritis and ulcerative colitis medicines Xeljanz (tofacitinib). This trial compared Xeljanz with another type of medicine used to treat arthritis called tumour necrosis factor (TNF) blockers in patients with rheumatoid arthritis. The trial's final results also showed an increased risk of blood clots and death with the lower dose of Xeljanz. FDA recommended revisions to the

Boxed Warning, FDA's most prominent warning, for Xeljanz to include information about the risks of serious heart-related events, cancer, blood clots, and death.

Recommendations for healthcare professionals include consideration of the benefits and risks for the individual patient before initiating or continuing therapy. In addition, to ensure the benefits of this medicine outweigh the risks in patients who receive them. It was also informed that FDA is limiting all approved uses to certain patients who have not responded or cannot tolerate one or more TNF blockers. Patients were advised to seek emergency medical attention if they experience signs and symptoms of a heart attack, stroke, or blood clot. Patients were also advised to tell their healthcare professionals about their history and risk factors for those events and seek emergency help immediately if they have any of those symptoms.

Previously, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in June, 2021 recommended an update to the product information for tofacitinib (Xeljanz®) to include a new recommendation for its use due to the risk of cardiovascular events and cancer. The PRAC reviewed that the data from a study conducted in patients who were 50 years of age or older with at least one additional cardiovascular risk factor and advised healthcare professionals that tofacitinib should only be used in patients over 65 years old, patients who are current or past smokers, patients with other cardiovascular risk factors and patients with other malignancy risk factors if no suitable treatment alternative is available.

The National Pharmacovigilance Centre (NPC) of the Drug Regulatory Authority of Pakistan has already issued Safety Alert No. 16, dated 10th September 2021, titled "risk *of serious heart-related events, cancer, blood clots, and death with Tofacitinib*" in light of US-FDA drug safety communication. As other stringent regulatory authorities have also updated their label/product information, therefore, the safety specification/label/prescribing information for Janus kinase (JAK) inhibitors in Pakistan may also be updated in Pakistan through PRAEC of the DRAP.

These JAK inhibitors are indicated for the treatment of chronic inflammatory diseases.

Xeljanz (tofacitinib) is used to treat certain serious, chronic, and progressive inflammatory conditions. It is approved to be used alone or with other drugs to treat rheumatoid arthritis (RA), a condition in which the body attacks its own joints, causing pain, swelling, joint damage, and loss of function. Xeljanz is also approved to treat psoriatic arthritis, a condition that causes joint pain and swelling; ulcerative colitis, which is a chronic, inflammatory disease affecting the colon; and polyarticular course juvenile idiopathic arthritis, a type of childhood arthritis. Xeljanz works by decreasing the activity of the immune system; an overactive immune system contributes to RA, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis.

Decision:

- ***The PRAEC decided as per Rule 10 (1) (h) (iv) and (vi) of Pharmacovigilance Rules that registration holders should update prescribing information/safety specification of Xeljanz ® (tofacitinib) with the inclusion of information related to heart attack or stroke, cancer, blood clots, and death in the warning and precaution section and to create a Boxed warning as per below format:***

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

- Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with XELJANZ/XELJANZ XR/XELJANZ Oral Solution if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test.
- Higher rate of all-cause mortality, including sudden cardiovascular death with XELJANZ vs. TNF blockers in rheumatoid arthritis (RA) patients.
- Malignancies have occurred in patients treated with XELJANZ. Higher rate of lymphomas and lung cancers with XELJANZ vs. TNF blockers in RA patients.
- Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with XELJANZ vs. TNF blockers in RA patients.
- Thrombosis has occurred in patients treated with XELJANZ. Increased incidence of pulmonary embolism, venous and arterial thrombosis with XELJANZ vs. TNF blockers in RA patients.

- ***To recommend Registration Board to update the prescribing information of Xeljanz ® (tofacitinib) in light of the decision of PRAEC and as per the label/prescribing information of Health Canada, MHRA-UK, US-FDA and PMDA Japan.***

3.5. Insomnia medicines: Risk of complex sleep behaviours.

The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Device Agency (PMDA) of Japan in July, 2022 have announced that the product information for triazolam, zolpidem, zopiclone and eszopiclone should be revised to include the risk of

abnormal behaviour as parasomnia. In addition, the use of triazolam, zolpidem or zopiclone is to be contraindicated in patients who have experienced abnormal behaviour such as parasomnia. Based on the published literature on the pharmacological mechanisms of parasomnia and cases of parasomnia reported in Japan, it was concluded the four drugs can increase the risk of abnormal behaviour as parasomnia, which may lead to serious self/other injuries or accidents. Also, a contraindication is considered necessary for triazolam, zolpidem and zopiclone in patients with a history of drug-induced parasomnia due to the risk of recurrence. Regarding eszopiclone, careful administration is still required but it is not a contraindication at this time, as there have been no reports of parasomnia in Japan for this drug.

Healthcare professionals were requested to ask patients and their families or other caregivers at the time of prescribing or dispensing of zolpidem tartrate, zopiclone, eszopiclone, or triazolam, as to whether the patients have experienced abnormal behaviour as a symptom of parasomnia after they used these drugs in the past. Examples of abnormal behaviour as a symptom of parasomnia include: Walking around indoors or outdoors; Driving a car; Making or eating a meal; Making a phone call; Behaving violently or calling out, etc. Most of the abnormal behaviours occur after the use of the drug without being fully awake, and those behaviours are not remembered the next day.

Previously**,** the United States Food and Drug Administration (US-FDA) in April 2019 has announced that rare but serious injuries have occurred with some medicines used to treat insomnia such as eszopiclone (Lunesta®), zaleplon (Sonata®) and zolpidem (Ambien®.). The injuries are a result of sleep behaviours which include: sleepwalking, sleep driving and engaging in other activities while not fully awake. These complex sleep behaviours have also resulted in deaths. Serious injuries and death from complex sleep behaviours have occurred in patients with and without a history of such behaviours, even at the lowest recommended doses, and the behaviours can occur after just one dose. These behaviours can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating such as tranquillizers, opioids, and anti-anxiety medicines. As a result, FDA required information about this risk to be added to the *Boxed Warning*, FDA's prominent warning and also to the *contraindication* (strongest warning) to avoid use in patients who have

previously experienced an episode of complex sleep behaviour with eszopiclone, zaleplon, and zolpidem.

Healthcare professionals were advised to not prescribe eszopiclone, zaleplon or zolpidem to patients who have previously experienced complex sleep behaviours after taking any of these medicines. Also, healthcare professionals should advise all patients that although rare, those behaviours have led to serious injuries or death and that if patients experience an episode of complex sleep behaviour, they should discontinue taking the medicines.

Triazolam, zolpidem, zopiclone and eszopiclone are indicated for insomnia and/or anaesthetic premedication.

Eszopiclone, Triazolam, zaleplon and zolpidem are medicines used to treat insomnia in adults who have difficulty falling asleep or staying asleep. They are a class of sedative-hypnotics and they work by slowing activity in the brain to allow sleep.

Decision:

- ***The PRAEC decided as per Rule 10 (1) (h) (ii), (iv) and (vi) of Pharmacovigilance Rules, 2022 that registration holders should update the prescribing information/safety specification of zolpidem-containing drugs by including information related to complex sleep behaviour in the warning and precaution sections, information related to contraindications in patients who have experienced complex sleep behaviours after taking these drugs in the past, and to create a boxed warning as per the following format:***

WARNING: COMPLEX SLEEP BEHAVIORS
Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of ***zolpidem***. Some of these events may result in serious injuries, including death. Discontinue ***zolpidem*** immediately if a patient experiences a complex sleep behavior

- ***To recommend Registration Board to update the prescribing of zolpidem-containing medicines in light of the decision of PRAEC and as per the label/prescribing information of US-FDA and PMDA Japan.***

3.6. Finasteride: Potential risk of suicidal ideation/thoughts & self-injury.

The Health Sciences Authority (HSA) of Singapore in August 2022 reminded healthcare professionals of the potential risk of suicidal ideation with the use of finasteride following results of a recent pharmacovigilance study that suggests younger patients with alopecia may be more vulnerable to the risk of suicide ideation. In the study, disproportionality analysis was used to assess whether suicidality or psychological adverse events (AEs) were more frequently reported for finasteride than would be expected by chance alone by comparing them against similar reports for all other drugs in VigiBase (WHO global database of ICSRs). The study identified 356 reports of suicidality and 2,926 reports of psychological AEs in users of finasteride, reported from 1993 to 2019. Among the reports with data available, the majority (99%) occurred in males, and 71% occurred in individuals aged between 18 and 44 years. Significant disproportionality signals for suicidality (reporting odds ratio [ROR], 1.63; 95% CI, 1.47-1.81) and psychological AEs (ROR, 4.33; 95% CI, 4.17-4.49) were identified in finasteride users. Healthcare professionals were advised to consider the potential risk of psychological adverse events when assessing the benefit-risk of finasteride for their patients.

On 19th of January, 2023, Health Canada through its summary safety review informed that it is working with the manufacturers to update the product safety information in the Canadian product monographs (CPM) for finasteride-containing products to strengthen the warning statements on the risks of suicidal ideation and self-injury, and to include information about patient screening for psychiatric risk factors prior to starting treatment, as well as continuous patient monitoring during and after stopping treatment. The safety review was triggered by the publication of a media article that discussed the potential risk of suicide in patients using Propecia (finasteride) for male pattern hair loss. Health Canada's review of the available information found a possible link between the use of finasteride and the risks of suicidal ideation and self-injury. At this time, there is not enough information to establish a link for the risk of suicide. However, strengthening of warning statements was warranted.

It was informed that Health Canada was monitoring the risk of suicidal ideation with the use of finasteride since 2012 and has completed 2 safety reviews in 2012 and 2015, and the information available at the time was considered too limited to determine whether there was a link between the use of finasteride and suicidal thoughts and behaviours (suicidality). In 2019, following reports of Canadian and international cases of suicide, suicidal ideation and

self-injury with the use of finasteride, the agency completed a third safety review that found a possible link between finasteride and the risk of suicidal ideation. The CPMs of finasteride were accordingly updated to include the risk of suicidal ideation.

Most recently in 2022, due publication of a media article that discussed the potential risk of suicide in patients using Propecia (finasteride) for male pattern hair loss, Health Canada completed a review of the risk of suicidal ideation and potential risks of suicide and self-injury with the use of finasteride. The purpose of the current review was to consider recent information and determine if additional measures were warranted. A review of the available information found a possible link between the use of finasteride and the risks of suicidal ideation and self-injury. At this time, there is not enough information to establish a link between the use of finasteride and the risk of suicide. Therefore, strengthening of warning statements on the risks of suicidal ideation and self-injury was warranted and Health Canada is working on it

Furthermore, the most recent Vigilyze statistics related to the finasteride and Standard MedDRA Query(SMQ) selected Depression and suicide/self-injury study identified 2,995 reports and 471 reports specifically with suicidal ideation. The larger portion of the reactions in known gender occurred in males (31.9%, and 45.6% in individuals aged between 18 and 44 years respectively, with the broader SMQ and specifically suicidal ideation. Significant disproportionality signals for suicidal ideation (reporting odds ratio [ROR], 10.6) and SMQ (ROR, 4.5) were identified.

Finasteride is indicated for the treatment of benign prostatic hyperplasia and androgenic alopecia

Decision:

- ***The PRAEC decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 that registration holders should update prescribing information/safety specification of Finasteride containing drugs by strengthening the warning statements on the risks of suicidal ideation and self-injury, and to include information about patient screening for psychiatric risk factors before starting treatment.***

- ***To recommend Registration Board to update the prescribing information of Finasteride-containing medicines in light of the decision of PRAEC and as per the product monograph/prescribing information of Health Canada.***

3.7. Pholcodine: Potential risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBA):

In September 2022**,** the European Medicines Agency (EMA) started a review of pholcodine following concerns that its use may put individuals at risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBAs) medicines. The review was requested by the French medicines agency (ANSM) following the preliminary results of a study carried out in France (ALPHO study). The results of the study suggested that taking pholcodine up to 12 months before general anaesthesia may increase the risk of having an NMBA-related anaphylactic reaction. The ALPHO study was carried out as a condition to the marketing authorizations of pholcodine-containing medicines following a previous safety review in 2011. At the time, the EMA's committee found no firm evidence on this risk and recommended that a new study should be carried out to investigate this risk. While the ALPHO study was ongoing, in 2021, a study in Australia linked pholcodine's use to an increased risk of anaphylaxis to NMBA muscle relaxants. This led to a recommendation by the PRAC of the EMA to include relevant warnings in the product information of pholcodine-containing medicines.

On 1 December 2022, the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA concluded its review of medicines containing pholcodine and recommended the revocation of the EU marketing authorisations for these medicines. During the review, the PRAC evaluated all available evidence including the final results of the ALPHO study, post-marketing safety data and information submitted by third parties such as healthcare professionals. The available data showed that the use of pholcodine in the 12 months before general anaesthesia with neuromuscular blocking agents (NMBA) is a risk factor for developing an anaphylactic reaction (a sudden, severe and life-threatening allergic reaction) to NMBAs. As it was not possible to identify effective measures to minimise this risk, nor to identify a patient population for whom the benefits of pholcodine outweigh its risks, pholcodine-containing medicines were being withdrawn from the EU market and will

therefore no longer be available by prescription or over-the-counter. Accordingly, healthcare professionals were advised to consider appropriate treatment alternatives and advise patients to stop taking pholcodine-containing medicines. Healthcare professionals were also advised to check whether patients scheduled to undergo general anaesthesia with NMBAs have used pholcodine in the previous 12 months, and remain aware of the risk of anaphylactic reactions in these patients.

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 14 December 2022. As the CMDh position was adopted by majority vote. The recommendations have been sent to the European Commission, which will issue a final legally binding decision applicable in all EU Member States.

Medicines containing pholcodine (an opioid medicine) are used in adults and children to treat non-productive (dry) cough and, in combination with other active substances, for the treatment of symptoms of cold and flu.

Discussion:

The committee deliberated the case as under:

- That the potential risk of developing anaphylactic reactions (a sudden, severe and life-threatening allergic reaction) to neuromuscular blocking agents (NMBAs) in patients with a previous history of Pholcodine use (12 months before general anaesthesia) is far greater than the use of latter product (Pholcodine) in cough and cold/flu preparation. This risk is greater considering the vulnerable population i.e. children and elderly in whom the event of falls, fractures and surgical procedures is of concern.
- The committee also discussed that at present it is not possible to identify the effective measures to minimize this risk in any age group, nor could identify a patient population in whom the benefits of pholcodine could outweigh its risks.
- The committee was apprised that the quota of pholcodine was allocated to registration holders by the DRAP in 2021 and a few brands may still be available in the market of Pakistan. It is also considered that a wide range of options for symptomatic treatment is available for the treatment of cough and flu.

Decision:

The PRAEC deliberated the case in detail and considered that at present there is a lack of possibility to identify effective measures to minimize the risk of anaphylactic reactions to neuromuscular blocking agents (NMBAs) in patients with a previous history of Pholcodine

use, and also considered the free availability of alternative treatment options for the treatment of cough and flu/cold in the market of Pakistan. Accordingly, the PRAEC decided to recommend to the Registration Board as per Rule 10(1)(h)(v) of Pharmacovigilance Rules, 2022 to suspend the registrations of "Pholcodine" containing products till the final outcome or decision by the European Commission, following which the case will be reconsidered

4. ADDITIONAL AGENDA

4.1. Reliance mechanism of DRAP in respect of Pharmacovigilance.

The committee was informed about Rule 10 (1) (h) of Pharmacovigilance Rules, 2022 related to reliance of Pharmacovigilance decisions in Pakistan. The said rule is reproduced as under:

> *The PRAEC shall consider or recognize and if deemed appropriate shall implement within Pakistan the pharmacovigilance relevant decisions of other countries and of regional and international bodies of the following nature, namely: -*
>
> *(i) modification or removal of an approved indication of therapeutic good due to safety reasons;*
>
> *(ii) addition of contraindications;*
>
> *(iii) imposition of post-authorization safety or efficacy studies due to safety reasons;*
>
> *(iv) major changes in the statements of warning, precaution or adverse reactions in the product information;*
>
> *(v) withdrawal or suspension of therapeutic goods in other countries due to safety reasons; and*
>
> (vi) *any other safety information or decision which it considers appropriate, for ensuring the safety of the public.*

However, it was noted that in the legal provisions of pharmacovigilance rules, 2022, the list of regulatory agencies and international bodies was not identified. In this regard, it was informed to the committee that Registration Board with the approval of DRAP has adopted reference regulatory authorities (Annex-B), that is also approved in DRAP document titled "Reliance Mechanism in Regulatory Processes "DRAP Approach on Good Reliance Practice", document no QMSC/GL/RM/005, dated 04-01-2023.

It was submitted to the committee that the same list of reference regulatory authorities and regional/international bodies should be adopted for pharmacovigilance relevant decision taken in respect of Rule 10 (1) (h) of Pharmacovigilance Rules, 2022 in Pakistan.

Decision:

The PRAEC adopted the list (Annex-B) of reference regulatory authorities, regional and international bodies for pharmacovigilance relevant decisions taken in respect of Rule 10 (1) (h) of Pharmacovigilance Rules, 2022 in Pakistan.

4.2. Pharmacovigilance Coordination with Provincial health departments.

The committee was informed about the pharmacovigilance system in the country as the National Pharmacovigilance Centre (NPC) is working under the Drug Regulatory Authority of Pakistan and is collecting adverse events from provincial pharmacovigilance centers, patients, healthcare professionals, public health programmes and registration holders. After collection, the data is validated, assessed and transferred to VigiBase (global database). If any signal is detected the same if presented before PRAEC for deliberation. It was informed that at present provincial pharmacovigilance centres of only the Punjab and Islamabad are functional and reporting the data to National centre. Federal Directorate of Immunization (FDI) is also submitting the data of adverse events following immunization to the National centre. All other provinces have notified their focal person pharmacovigilance, but have not started submitting their data.

Decision:

The PRAEC decided that in the next meeting of PRAEC, focal persons of pharmacovigilance of every province/administrative territory may be invited to present the status of the pharmacovigilance system in their provinces/territory along with the way forward for earlier implementation of pharmacovigilance rules, 2022.

4.3. Med Safety Mobile Application

Med Safety Application is a mobile application (android and iOS platform) for patients and healthcare professionals to report adverse drug reactions and adverse events following immunization which are received directly in VigiFlow and also give access to safety alerts published by the National Pharmacovigilance Centre of the DRAP.

The Committee discussed the statistics regarding users of the Med Safety Application. It was apprised that the number of users of the application should be improved through raising awareness. This at first instance can be disseminated among the officers and officials of DRAP.

Decision

The PRAEC advised Pharmacy Services Division to take necessary steps to increase the use of the Med Safety Mobile Application in Pakistan.

ANNEX A:

(Proforma-D) for expert members of boards/committees

AFFIDAVIT FOR NON-EXISTANCE OF CONFLICT OF INTEREST

I_____S/D/W/O_____

having CNIC No._____ resident of_____

serving in Drug Regulatory Authority of Pakistan as Member of _____,

solemnly affirm and declare on oath :-

1. That I do not have any financial or professional conflict of interest.

2. That whatever has been stated above is true to the best of my knowledge and belief and nothing has been concealed thereof. If anything is found to be contrary to the above declaration I shall be solely held responsible and liable for legal action.

DEPONENT

Signature: _____

Name: _____

Designation: -_____

Date: -_____

ANNEX B:

LIST OF REFERENCE REGULATORY AUTHORITIES

Sr#	Country	Regulatory authority
1.	USA	Food & Drug Administration (FDA)
2.	Canada	Health Canada
3.	Australia	Therapeutic Goods Administration (TGA)
4.	Japan	Pharmaceuticals and Medical Devices Agency (PMDA)
5.	UK	Medicines and Healthcare Regulatory Agency (MHRA)
6.	France	National Agency for the Safety of Medicine and Health Products (ANSM)
7.	Germany	Federal Institute for Drugs and Medical Devices
8.	Netherland	Medicines Evaluation Board
9.	Switzerland	Swissmedic
10.	Austria	Austrian Agency for Health and Food Safety
11.	Denmark	Danish Medicines Agency
12.	Sweden	Medical Products Agency
13.	Norway	Norwegian Medicines Agency
14.	Belgium	Federal Agency for Medicines and Health Products
15.	Finland	Finnish Medicine Agency
16.	Italy	Italian Medicine Agency (AIFA)
17.	Ireland	Health Products Regulatory Authority (HPRA)
18.	Iceland	Icelandic Medicine Agency
19.	Spain	Spanish Agency for Medicines and Health Products
20.	Europe	European Medicines Agency (EMA)
21.	WHO	World Health Organization