MINUTES OF THE 1ST MEETING OF PHARMACOVIGILANCE RISK ASSESSMENT EXPERT COMMITTEE

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

File No: 17-1/2022-PRAEC(PS)

OCTOBER 12, 2022
DRUG REGULATORY AUTHORITY OF PAKISTAN
Telecom Foundation Complex, 7th Mauve Area, G-9/4, Islamabad

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Minutes of the 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee.

1st 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 12th of October, 2022. The meeting was attended by the following members:

S. No	Name	Designation
1	Brig. (R) Dr. Akbar Waheed	Chairman, PRAEC, Professor, Islamic International College, Rawalpindi,
2	Dr Noor Muhammad Shah	Co-Chair, PRAEC Director, Division of Pharmacy Services, DRAP.
3	Malik Muhammad Asad	Secretary, PRAEC Deputy Director, Division of Pharmacy Services
4	Prof. Dr. Madeeha Malik	Professor, Pharmacy Practice, Hamdard Institute of Pharmaceutical Sciences, Hamdard University, Islamabad
5	Prof. Dr. Arif-Ullah Khan	Dean, Riphah Institute of Pharmaceutical Sciences, Riphah International University, Islamabad.
6	Shoukat Sahad	Chief Pharmacist, Rehman Medical Institute (RMI), Peshawar.
7	Prof. Dr. Ghulam Murtaza Gondal	Professor, Department of Medicine, Foundation University Medical College Rawalpindi.
8	Mr. Muhammad Taimoor Chaudhary	Section Supervisor (Drug Chemistry Unit), Punjab Forensic Science Agency, Lahore
9	Syed Shamim Raza	Director, Services Line and Chief, Pharmacy Services, Agha Khan University Hospital, Karachi
10	Dr. Khalid Mehmood	Associate Prof./Head of Pharmacy, Department of Pharmacy, Abbottabad University of Science & Technology, Abbottabad.

Meeting of the Committee was started with the recitation of the Holy Quran and salutation upon the Holy Prophet (P.B.U.H).

The members of the Committee introduced their selves with a brief regarding their qualifications, experience and their expertise in the field of risk assessment.

1. INTRODUCTION AND BRIEF

1.1. Welcome Note & Brief by the Head of the National Pharmacovigilance Centre.

After the completion of the introduction of the participants, the Head of the National Pharmacovigilance Centre, Dr Noor Muhammad Shah welcomed the participants on behalf of the National Pharmacovigilance Centre (NPC), Division of Pharmacy Services and Drug Regulatory Authority of Pakistan (DRAP). He apprised the members of the Committee regarding the importance of the Committee and its role in patient safety. He elaborated that members have been assigned the prestigious task as per their expertise and knowledge in the matter. He hoped that the members would fulfil their responsibilities in the subject matter.

The Head of the National Pharmacovigilance Centre, Director of the Division of Pharmacy Services also briefed the members regarding the pharmacovigilance process, the process of monitoring the safety of therapeutic goods by the DRAP, the current structure of the pharmacovigilance system in Pakistan consisting of the National Pharmacovigilance Centre, Provincial Pharmacovigilance Centres, Federal Immunization Programme Centres and the sub-regional pharmacovigilance centres along with the way forward of the pharmacovigilance activities to be undertaken.

1.2. Comments/ Remarks of Chair, PRAEC.

The Chairman, PRAEC appreciated the constitution of the Committee for monitoring medicine's safety (adverse drug reactions and risks) which was the need of the hour and that the DRAP has taken the right step in this regard. The Chairman also applauded the Division of Pharmacy Services, DRAP for taking untiring efforts to achieve the sacred goal of patient safety.

1.3. Detailed presentation about the working of the National Pharmacovigilance Centre and PRAEC.

A detailed presentation about the working of the National Pharmacovigilance Centre (NPC) and Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was delivered by Focal

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

The Focal Person of the National Pharmacovigilance Centre also apprised the members regarding the constitution and composition of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC). He also informed members about the history of pharmacovigilance in Pakistan and its progress after the establishment of DRAP. He informed the members that Pharmacovigilance Rules have been notified, guidelines have been prepared, and multiple workshops have been arranged. The stakeholders have been informed regarding the reporting of adverse events to the various centres/channels. He told that National Pharmacovigilance Centre has been integrated with WHO Collaborating Centre, i.e. Uppsala Monitoring Centre. Reports of adverse events are being collected through different channels that will be presented before the PRAEC committee for its assessment.

The PRAEC appreciated the work of NPC. However, it was advised that NPC should strengthen its human resources to ensure the safety of the 220 million population of Pakistan. It was also advised that officers/staff of various expertise such as Physicians, Pharmacists, Pharmacoepidemiologists and Biostatisticians should be hired in this regard

1.4. Statement of Commitment by the members of the committee.

The members of the Committee accordingly declared their commitment as under:

That they will maintain secrecy in the matter as per law, and if not required will not disclose the information received in the matter. They will work in the public interest for the well-being and safety of patients.

That, they will not strive for personal propagation, for the propagation of any association or institution and will work and show loyalty to the DRAP in respect of decisions taken in respect of Pharmacovigilance, and working in the public interest and they will stick to the scope and mandate of the PRAEC as per the TORs of the committee and Rules.

1.5. 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. On the same pattern,

Members/Experts of the Pharmacovigilance Risk Assessment Expert Committee of the DRAP have to ensure and 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.

Decision of PRAEC:

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.

1.6. Standard Operating Procedure for Pharmacovigilance Risk Assessment Expert Committee (PRAEC).

The Standard Operating Procedure (SOP) for the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) prepared by the National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP) **(Annexure B)** was presented before the Committee.

Decision of PRAEC:

The Committee appreciated the work done and endorsed the Standard Operating Procedure (SOP) for the working of PRAEC (Annexure-B,) prepared by the National Pharmacovigilance Centre for onward processing as per the procedures of the DRAP.

2. DOMESTIC SIGNALS

2.1. Anaphylactic Reaction with Diclofenac Sodium.

Introduction

Diclofenac Sodium through the intra-muscular route is effective in acute forms of pain, including renal colic, exacerbations of osteo- and rheumatoid arthritis, acute back pain, acute gout, acute trauma and fractures, and postoperative pain. Diclofenac sodium is an NSAID that exhibits anti-inflammatory, analgesic and antipyretic effects. The mechanism of action may involve the inhibition of prostaglandin synthesis by inhibiting the cyclooxygenase (COX-1 and COX-2) pathways.

An anaphylactic reaction is an acute hypersensitivity/allergic reaction of the immediate type, characterized by one or more of symptoms including itching, erythema, urticaria, angioedema, laryngeal oedema or spasm, bronchospasm, hypotension, abdominal cramps, diarrhoea, anxiety, agitation and loss of consciousness. This type of reaction may result from either immunological (anaphylactic) or non-immunological (anaphylactoid) mechanisms, resulting in the liberation of histamine and other mediators. When it is the cardiovascular system that is predominantly involved in an anaphylactic reaction, shock may occur, manifested typically by tachycardia or bradycardia, pulselessness, hypotension, psychological signs of adrenergic stimulation (such as anxiety), and signs of cerebral ischaemia (loss of consciousness). When a reaction affects predominantly the respiratory system, life-threatening laryngeal oedema or refractory bronchospasm may occur (with or without shock).

Reports & Background:

The National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP) through the Provincial Pharmacovigilance Centre (PPC), Directorate of Drugs Control Punjab received two serious cases of anaphylactic reactions upon STAT dose administration of injection Diclofenac Sodium 75mg/3ml intramuscular (IM). The cases were reported by Clinical Pharmacy and Pharmacovigilance Officers (CPPOs) of two public sector hospitals in Punjab.

Case 1 was related to 38 years old male patient, who was prescribed the diclofenac sodium injection for wound pain on the left leg on 02-01-2022. Upon administration of injection of diclofenac sodium IM x STAT, the patient developed an Anaphylactic Shock immediately. Symptoms observed were pruritus, erythema, sweating, apprehension and fainting due to a sudden drop in blood pressure. The drug was stopped and the treatment initiated and accordingly patient was revived.

Case 2 was related to a 30-year-old asthmatic female patient who was presented with a complaint of backache. Immediately after the injection of diclofenac sodium on 25-01-2022, the patient developed serious reactions of severe shortness of breath, wheezy chest, hypoxia and hypotension. She was treated in the hospital and later transferred to a private hospital where she was diagnosed to have a hypersensitivity reaction to diclofenac sodium. After proper treatment in the hospital, later on after recovery, she was discharged

The two cases of Diclofenac Sodium injection-associated anaphylactic reactions were discussed in the 10th meeting of the Provincial Pharmacovigilance Centre of the Punjab's Adverse Drug Reaction Scrutiny Committee (ADRSC) held on 25-03-2022. The ADRSC recommended reporting the cases to the Drug Regulatory Authority of Pakistan (DRAP) for detailed investigation and if necessary for an update in prescribing information/ label of Diclofenac Sodium with warning signs of anaphylactic reactions (anaphylactic shock).

Assessment at National Pharmacovigilance Centre.

The National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, Drug Regulatory Authority accordingly assessed the cases. The adverse drug reactions were categorized as "Possible" and "Probable" based on plausible time to onset (same day immediately after administration), positive dechallenge (recovered on withdrawing) and unable to explain from other drugs/ disease.

The NPC also noted that anaphylactic reactions/ shock and its sign and symptoms (those reported in the instant cases) are already listed in the label approved by the United States Food and Drugs Administration(US-FDA) and Summary of Product Characteristics of Medicine and Health Product Agency of United Kingdom. There is also significant disproportionality in the global database for the Drug-ADR combination (diclofenac and anaphylactic reaction/shock) as it has a positive IC025 value along with increased ROR and PRR value > 1 that showed a potential association. Likewise, there was also published research about cases of severe anaphylactic reactions/ hypersensitivity/ anaphylaxis with diclofenac sodium injection. Based on the assessment performed at the NPC level and recommendations by the provincial pharmacovigilance centre, the cases were presented before the PRAEC for consideration under Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022.

Decision of PRAEC:

i. ***The PRAEC after detailed deliberation and discussion decided to update the warning, precaution & contraindication sections of the prescribing information/ safety specification/ label of Diclofenac Sodium injection about the occurrence of anaphylactic reaction/ anaphylactic shock and its contraindication in a patient with a history of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs.***

ii. Furthermore, the PRAEC in light of Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 decided to recommend the Registration Board to update the safety specification/ label of Diclofenac Sodium Injection.

2.2. Infusion-related hypersensitivity reactions with Remdesivir

Introduction:

Remdesivir is an antiviral drug that belongs to the group nucleoside analog. It is a competitive inhibitor of viral RNA-dependent RNA polymerase thus inhibiting viral RNA synthesis during the reverse transcription phase. The antiviral activities of Remdesivir on RdRp have been reported against Ebola virus, MERS-CoV, SARS-CoV, and other coronaviruses such as CoV-OC, CoV-229E, and PDCoV.

Infusion-related reactions (IRRs) have been reported as anaphylaxis, anaphylactoid reactions and cytokine release syndrome. IRR(s) is/ are any sign (s) or symptom(s) experienced by patients during the infusion of pharmaceutical or biological agents or any event occurring on the first day of drug administration. Hypersensitivity reactions may be specific to drug classes and biological agents.

All infusion-related reactions involve the immune system; however, some (anaphylactic) are allergic in nature and usually are mediated by immunoglobulin E (IgE), whereas others (anaphylactoid) are not true allergic reactions and are not mediated by IgE.

Non-IgE-mediated "pseudoallergic" reactions are primarily caused by (1) certain liposomal formulations of intravenous drugs and imaging agents, (2) liquid infusion containing micelle-forming amphiphilic lipids or synthetic block-copolymer emulsifiers, and (3) iodinated radiocontrast media with limited solubility in water. Common features of the latter "pseudo allergens" include the capacity to activate the complement (C) system; also, the symptoms they cause are often typical manifestations of excessive anaphylatoxin generation in blood. Hence, these reactions have been called "C activation-related pseudoallergy" (CARPA).

Most patients who exhibit infusion-related reactions can be rechallenged either by changes to premedications or through desensitization protocols.

Reports & Background:

The National Pharmacovigilance Centre received a cluster of three serious (life-threatening) adverse drug reaction reports from a hospital with inj Viso-REM (Remdesvir) (Batch# 21H032) manufactured by M/s Vision Pharmaceutical Pvt Limited and marketed by M/s Global Pharmaceutical Islamabad. The events of tachycardia, dyspnoea, chills and pyrexia were noted after the use of Remdesivir through an intravenous drip (200 mg stat then 100 mg/day for four days) for COVID-19 Pneumonia, with time to onset as 0 days. The drug was withdrawn after the occurrence of events in all cases and the patients recovered the same day. It was suspected by the reporter that these ADRs might be caused either due to quality problems or adverse events.

The National Pharmacovigilance Centre labelled it as a potential signal of infusion-related hypersensitivity reactions. However, the reports were a cluster in nature having similar adverse events, the same drug and its batch and reported within a short period from the same place, which triggers suspicion of a quality problem as suspected by the reporter. Therefore, the National Pharmacovigilance Centre decided to carry out the quality testing of the said batch of Inj Viso-REM (Remdesvir).

Accordingly, a panel consisting of area Federal Inspector Drugs (FID-I) along with Assistant Directors, QA & LT Division of DRAP visited M/s Vision Pharmaceuticals Plot No. 22-23, Industrial Triangle Kahuta Road Islamabad DML No. 000517 (by way of Formulation) for inspection and collection of sample for quality testing. The panel took a sample of the suspected batch i.e. 21H032 along with two more batches i.e. 21H061 and 21J014 for testing or analysis by the Central Drugs Laboratory (CDL) of the DRAP. Subsequently, all the three samples including the suspected batch 21H032 were declared of standard quality with regard to the tests performed by CDL-DRAP. However, during the inspection/ investigation of the premises, the panel made some observations of non-compliance with standard operating procedures. Based on these observations, the panel recommended that Registration Board may be requested to review the grant of Emergency Use Authorization for the product Viso-Rem Solution for Infusion manufactured by M/s Vision Pharmaceuticals Plot No. 22-23, Industrial Triangle Kahuta Road Islamabad and advised the firm to halt production of Viso-Rem Injection.

Assessment by National Pharmacovigilance Centre.

The causality assessment of all the three cases has been performed by the Causality Assessment Group of the National Pharmacovigilance Centre and all three cases have been assessed to have a possible relationship with drug intake. Hypersensitivity reactions, including infusion-related and anaphylactic reactions, are listed as adverse reactions of Remdesivir in the FDA label. The hypersensitivity reactions include all the instant reported events, reported by the hospital in Pakistan such as tachycardia, dyspnoea, chills and pyrexia. The warnings and precautions sections of Remdesivir label/ SmPc published by US-FDA and MHRA state that hypersensitivity including infusion-related and anaphylactic reactions have been observed following administration of the drug mostly within one hour. The range of signs and symptoms of hypersensitivity included in the label are hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, diaphoresis and shivering. Administering the drug at slower infusion rates i.e. up to 120 minutes has been advised in the FDA label that can potentially prevent the occurrence of these symptoms. Monitoring patients during infusion and observing patients for at least one hour after the infusion is completed for signs and symptoms of hypersensitivity is also advised. On the occurrence of clinically significant hypersensitivity reactions, it has been advised that the drug administration should be immediately discontinued and proper treatment for hypersensitivity should be initiated. Furthermore, as per the statistics of the global database, there is significant disproportionality and the potential association between the Drug-ADR combination (Remdesivir and Infusion related hypersensitivity reactions) as evident by positive IC025 value along with ROR and PRR value > 1. Based on the assessment and evaluation done at the level of NPC, the cases were presented before PRAEC in light of Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 for its consideration.

Decision of PRAEC

The PRAEC after detailed deliberation & discussion and in light of recommendations of the National Pharmacovigilance Centre decided as under:

i. ***To update the prescribing information/ safety specification/ label of Remdesivir with the inclusion of information related to infusion-related hypersensitivity reactions and its monitoring in the warning and precaution sections and onward recommendation to the Registration Board in light of Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022. Furthermore, all the registration holders should***

also introduce educational training for healthcare professionals on proper preparation, administration and flow rate of Remdesivir, and monitoring of patients;

ii. ***To advise the Registration Board to review the grant of Emergency Use Authorization for the product Viso-Rem Solution for infusion in light of the investigation carried out by the panel of QA and LT Division of the DRAP; and***

iii. ***Furthermore, to advise the QA and LT Division of the DRAP in light of Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022 to strengthen its surveillance mechanism of registration holders of Remdesivir.***

3. RELIANCE OF INTERNATIONAL SAFETY DECISIONS.

3.1. Clozapine: Risk of serious bowel complications

The Therapeutic Goods Administration (TGA) of Australia on 22nd, April 2022 through a safety advisory informed that Product Information (PI) and Consumer Medicine Information (CMI) for Clozapine have been updated to strengthen warnings about potential severe gastrointestinal side effects, including constipation. It was informed that Clozapine may also affect the bowels by slowing them down and can cause severe constipation, the condition known as clozapine-induced gastrointestinal hypomotility. If untreated, it can lead to serious problems. Consumers who were using clozapine were informed to look out for changes in their bowel function and to contact their health professionals if they develop any of the symptoms.

On 14th January 2022, the United States Food and Drug Administration (US-FDA) through Drug Safety Podcast referred to the already issued communication dated 18th of February, 2020 where the FDA strengthens the existing warning that untreated constipation caused by schizophrenia medicine clozapine (Clozaril®) can lead to serious bowel problems. It was informed that serious bowel complications can lead to hospitalization or even death if constipation is not diagnosed and treated quickly.

Patients were advised to contact their healthcare professionals if they have symptoms that can be associated with serious bowel problems such as nausea, vomiting or stomach pain. To

prevent constipation, they should eat more fruits, vegetables, and grains that are high in fibre; drink plenty of water and other liquids, and get enough exercise.

Healthcare professionals were advised the following: to evaluate bowel function before starting a patient on clozapine and avoid co-prescribing clozapine with other anticholinergic medicines that can cause gastrointestinal hypomotility; advise patients frequently of the significant risk of constipation and life-threatening bowel issues and the need to stay hydrated to prevent constipation; advise patients to contact a health care professional right away if they have difficulty having a bowel movement or passing stools, do not have a bowel movement at least three times a week or less than their normal frequency

Clozapine is a medicine that has been used for more than 40 years to treat schizophrenia in patients whose symptoms are not controlled with standard treatment.

Decision of PRAEC

i. ***The PRAEC after detailed deliberation and discussion decided to update and strengthen the warning section of Clozapine with gastrointestinal side effects, including constipation and severe bowel problem in light of Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022.***
ii. ***It was decided to onward recommend/inform the Registration Board for necessary action in the matter.***

3.2. Iodinated contrast media (ICM) injections: Risk of Hypothyroidism in babies and young children.

On 30th March, 2022, the United States Food and Drug Administration (US-FDA) through a Drug Safety Communication informed that they have approved a new warning to the prescribing information for the entire class of iodinated contrast media (ICM) injections and monitoring recommendations for children 3 years or younger. The warning describes the risk of an underactive thyroid or a temporary decrease in thyroid hormone levels. These risks and recommendations pertain to ICM given as an injection through an artery or vein. Newborns, particularly those born premature, and children in their first 3 years with underlying conditions such as heart issues may be at higher risk for problems with the thyroid. It was informed that the agency first alerted the public about cases of underactive thyroid in infants receiving ICM

back in 2015 and now six new research studies evaluating this risk have been published. The FDA has concluded based on their review of the published studies that there is compelling evidence of a significant risk for an underactive thyroid or a temporary decrease in thyroid hormone levels in newborns and children through 3 years after exposure to ICM. Back in December 2017, the Medicines and Medical Devices Safety Authority (Medsafe) of the Newzealand also requested that data sheets for iodine-containing contrast agents (ICAs) to be updated with information on the risk of hypothyroidism, particularly in neonates and should include advice on thyroid monitoring.

ICM are drugs containing iodine that are given to patients to enhance the ability to see blood vessels, organs, and tissues on medical images such as X-rays or computed tomography (CT) scans, thus helping healthcare professionals to diagnose potential problems. Examples include iohexol (Omnipaque), iopromide (Ultravist 300, 370) and iodixanol (Visipaque 270, 320) etc. Common side effects associated with ICM include flushing in the face, nausea or vomiting, mild itchiness, and skin rash.

Parents and caregivers of a child below 3 years and receiving ICM injections should talk with healthcare professionals for additional information. If the child is a newborn, has very low birth weight, was premature, has a heart condition, or was admitted to a neonatal or pediatric intensive care unit, they may be at higher risk of developing underactive thyroid or a temporary decrease in thyroid hormone levels. Babies and young children typically do not show any visible signs of thyroid problems and may need to be monitored by their healthcare professionals after receiving ICM.

Healthcare professionals should perform appropriate monitoring of patients from birth through 3 years for the possibility of hypothyroidism or a temporary decrease in thyroid hormone levels following exposure to ICM. Healthcare professionals should consider evaluating thyroid function within 3 weeks, especially in term and preterm neonates and children with some underlying conditions. If thyroid dysfunction is detected, it should be properly treated and monitored as clinically needed to avoid future cognitive and other developmental disabilities. Increased-risk pediatric patients include those who are newborns or have very low birth weight, prematurity, or the presence of cardiac or other conditions such as those requiring care in neonatal or pediatric intensive care units. Patients with cardiac

conditions may be at the greatest risk since they often require high doses of contrast during invasive cardiac procedures. These increased-risk pediatric patients require close monitoring.

Decision of PRAEC

i. ***The PRAEC after detailed deliberation and discussion decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 to update the warning and precaution section of the prescribing information of the entire class of iodinated contrast media (ICM) that are used for radiological purposes to include risks of an underactive thyroid or a temporary decrease in thyroid hormone levels in children 3 years or younger i.e newborns, particularly those born premature, and children in their first 3 years with underlying conditions such as heart issues etc***

ii. ***It was decided to onward recommend/inform the Registration Board for necessary action in the matter.***

3.3. Remdesivir: Risk of sinus bradycardia

Health Canada in August, 2021 announced that it will work with the manufacturer of Remdesivir to update the product information to include a warning on the potential risk of sinus bradycardia. Health Canada assessed case reports of sinus bradycardia in patients receiving Remdesivir in their database and in the literature and concluded that a link between the use of Remdesivir and the risk of sinus bradycardia is possible.

Previously, in June, 2021, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) recommended a change to the product information for Remdesivir (Veklury®) to include sinus bradycardia as an adverse drug reaction. The PRAC reviewed available data on rare reported cases of bradycardia in patients treated with Remdesivir as well as data from clinical trials and the scientific literature. The PRAC concluded that a causal relationship between the use of Remdesivir and the event is reasonably possible and recommended the revision of the product information. The majority of the events of sinus bradycardia resolved a few days after the treatment with Remdesivir was discontinued.

Remdesivir is an antiviral medicine that is indicated to treat COVID-19 in adults and adolescents with pneumonia requiring supplemental oxygen.

Sinus bradycardia occurs when the heart beats slower than normal. Sinus bradycardia can very rarely cause symptoms, such as dizziness, tiredness, shortness of breath, and chest discomfort.

Decision of PRAEC

i. ***The PRAEC after discussion decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 to update the prescribing information (warning & adverse drug reactions sections) of Remdesivir to include the potential risk of sinus bradycardia.***
ii. ***It was decided to onward recommend/inform the Registration Board for necessary action in the matter.***

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

The National Pharmaceutical Regulatory Agency (NPRA) of Malaysia in April, 2021 has announced that the product information for atezolizumab (Tecentriq®) has been updated to include the risk of severe cutaneous adverse reactions (SCAR). Based on analysis from the company's global safety data of 99 cases of SCARs identified globally, of which 36 cases were confirmed by histopathology or specialist diagnosis.

The Medicines and Healthcare Products Regulatory Agency (MHRA) in June, 2021 also announced that the product information for atezolizumab (Tecentriq®) has been updated to include information about the risk of severe cutaneous adverse reactions (SCARs), which includes Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN). SCARs were previously known to be potentially associated with the use of atezolizumab. A review of safety data for atezolizumab and the risk of SCARs was recently completed in Europe. Based on this review SCARs are an identified risk for atezolizumab. Also, other products used for cancers in the same class as atezolizumab, including cemiplimab, ipilimumab, nivolumab and pembrolizumab list SCARs as possible adverse effects in the Summary of Product Characteristics (SmPC). Healthcare professionals should monitor patients for signs and symptoms of severe skin reactions and exclude other causes. In addition, Direct Healthcare Professional Communication (DHPC) were also issued by the manufacturers in New Zealand and European Medicine Agency back in November, 2020.

SCARs are a heterogeneous group of delayed hypersensitivity reactions. These events mainly consist of acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) and can be potentially life-threatening, and lead to severe, potentially chronic sequelae.

Atezolizumab is an immunostimulatory drug indicated to treat non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, urothelial carcinoma and triple-negative breast cancer.

Decision of PRAEC

i. ***The PRAEC after deliberation decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 to update prescribing information of Atezolizumab (Tecentriq®) to include the risk of severe cutaneous adverse reactions (SCAR) including Stevens-Johnsons Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).***
ii. ***Furthermore, it was decided that registration holders should issue direct healthcare professional communication in this regard.***
iii. ***It was decided to onward recommend/inform the Registration Board for necessary action in the matter.***

3.5. Metformin and reduced vitamin B12 levels

The Medicine and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom on 20th June, 2022 through a drug safety update informed that decreased vitamin B12 levels, or vitamin B12 deficiency, is now considered a common side effect in patients on metformin treatment, especially in those receiving a higher dose or longer treatment duration and in those with existing risk factors. It was informed that the known adverse drug reaction of vitamin B12 deficiency was recently reviewed for the brand leader Glucophage (metformin) within Europe with input from the MHRA. After this review, the MHRA agreed that the product information for patients and healthcare professionals for medicines containing metformin should be updated to state that vitamin B12 deficiency is a common adverse drug reaction, and may affect up to 1 in 10 people who take it. The product information for other medicines containing metformin will also be updated including fixed-dose combination products containing metformin

The product information has also been updated to note that the risk of this adverse reaction occurring increases with increasing metformin dose and treatment duration and in patients with risk factors known to cause vitamin B12 deficiency such as:

i. baseline vitamin B12 levels at the lower end of the normal range;

ii. conditions associated with reduced vitamin B12 absorption (such as elderly people and those with gastrointestinal disorders such as total or partial gastrectomy, Crohn's disease and other bowel inflammatory disorders, or autoimmune conditions);

iii. diets with reduced sources of vitamin B12 (such as strict vegan and some vegetarian diets);

iv. concomitant medications that are known to impair vitamin B12 absorption (including proton pump inhibitors or colchicine); and

v. genetic predisposition to vitamin B12 deficiency, such as intrinsic factor receptor deficiency (Imerslund-Gräsbeck syndrome) and transcobalamin II deficiency.

Healthcare professionals were advised to test vitamin B12 levels in those presenting with anaemia or neuropathy and that periodic vitamin B12 monitoring should be considered in patients with risk factors for vitamin B12 deficiency.

Decision of PRAEC

i. The PRAEC after discussion decided as per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022 to update prescribing information of Metformin and other medicines containing Metformin to state that vitamin B12 deficiency is an adverse drug reaction with Metformin use and the risk of this adverse reaction occurrence increases with increasing metformin dose and treatment duration and in patients with risk factors known to cause vitamin B12 deficiency.

ii. It was decided to onward recommend/inform the Registration Board for necessary action in the matter.

3.6. Pregabalin: Risk of Major Congenital Malformations

The Medicine and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom on 19th April, 2022 announced that the product information for pregabalin will be updated to include information from a new study which has suggested pregabalin may slightly increase

the risk of major congenital malformations if used in pregnancy. The MHRA reviewed the results of a Nordic observational study that consisted of 2,700 pregnancies exposed to pregabalin in the first trimester, alongside a recent European review which had the same conclusions. The study showed a higher prevalence of major congenital malformations in the babies (live or stillborn) exposed to pregabalin in the first trimester of pregnancy compared with those not exposed to pregabalin or any other antiepileptic drug.

The review concluded that pregabalin's use during the first trimester of pregnancy may cause a slight increase in the risk of major congenital malformations in the unborn child. Furthermore, the Health Products Regulatory Authority (HPRA) of Ireland back in February 2022 also recommended that product information of pregabalin along with other anti-epileptic drugs be updated based on the evidence of risks associated with in-utero exposure to these drugs. The product information of pregabalin continues to advise that effective contraception should be used during treatment and that use in pregnancy should be avoided unless it is necessary.

Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalization, and for generalized anxiety disorder in adults.

Decision of PRAEC

i. ***The PRAEC after detailed deliberation and discussion decided as per Rule 10 (1) (h) (iv) and (vi) of Pharmacovigilance Rules, 2022 to update prescribing information of Pregabalin to include information from a new study that pregabalin may slightly increase the risk of major congenital malformations if used in pregnancy and include advise on effective contraception during treatment in pregnancy.***
ii. ***It was decided to onward recommend/inform the Registration Board for necessary action in the matter.***

3.7. Interaction between hydroxychloroquine or chloroquine, and macrolide antibiotics: increased risk of cardiovascular events with co-administration.

The MHRA on 15th February, 2022 announced that the product information for hydroxychloroquine, chloroquine and macrolide antibiotics (azithromycin, erythromycin or clarithromycin) will be revised to include the increased risk of cardiovascular events and

cardiovascular mortality if hydroxychloroquine or chloroquine is taken with a macrolide-antibiotic. A review was conducted by the Pharmacovigilance Expert Advisory Group of the Commission on Human Medicines following the results of a retrospective observational study which shows that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events (including angina or chest pain and heart failure) and cardiovascular mortality.

It was recommended in the review that the product information for hydroxychloroquine and systemic azithromycin medicines should be amended to include new warnings and advice on these risks. Owing to the similar safety profiles, the risks with concurrent use of hydroxychloroquine and azithromycin were considered to apply to concurrent use of hydroxychloroquine and other systemic macrolide antibiotics (clarithromycin or erythromycin) and to the use of chloroquine with systemic macrolide antibiotics. Therefore, the review recommended that similar warnings should also be added to the product information for chloroquine and for systemic clarithromycin or erythromycin. However, these warnings were not being introduced for topical macrolide products (which are indicated for conjunctivitis or acne).

The MHRA also reminded the healthcare professionals that the product information for hydroxychloroquine and chloroquine already contains warnings about cases of cardiomyopathy resulting in cardiac failure, in some cases with fatal outcomes. It was also informed that evidence suggests both hydroxychloroquine and chloroquine can prolong the QT interval, especially in overdose or when used in combination with other medicines with the potential to induce cardiac arrhythmias. Likewise, warnings are also in place across the product information for azithromycin, clarithromycin, and erythromycin to use caution in patients with a history of QT interval prolongation or in patients receiving a medicine known to cause QT prolongation. Although the mechanism of the observed effects was not examined in detail by the study, it was proposed that events could have been caused by cumulative effects of hydroxychloroquine and azithromycin on the QT interval, potentiating arrhythmias and cardiac death, or through other additive cardiotoxic effects more generally.

Hydroxychloroquine is indicated for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and dermatological conditions aggravated by sunlight. Chloroquine is indicated for malaria prophylaxis or treatment and other indications. It was advised that

healthcare professionals should carefully consider the benefits and risks before prescribing macrolide antibiotics to patients being treated with hydroxychloroquine or chloroquine.

Decision of PRAEC

i. ***The PRAEC after discussion decided as per Rule 10 (1) (h) (iv) and (vi) of Pharmacovigilance Rules, 2022 to update prescribing information (warning and interaction sections) of hydroxychloroquine, chloroquine and macrolide antibiotics (azithromycin, erythromycin or clarithromycin excluding topical macrolides) about the potential interaction of increased risk of cardiovascular events and cardiovascular mortality if hydroxychloroquine or chloroquine is taken with a macrolide-antibiotic.***

ii. ***It was decided to onward recommend/inform the Registration Board for necessary action in the matter.***

3.8. Hydroxyethyl-starch solutions for infusion: risk of kidney injury and death.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) on 11th February, 2022 recommended that the market authorization of hydroxyethyl-starch (HES) solutions for infusion should be suspended across the European Union. These solutions for infusion products are indicated as an addition to other treatments for plasma volume replacement following acute (sudden) blood loss.

The safety of these solutions for infusion was reviewed in 2013, and a number of restrictions and measures to minimise the risk of kidney injury and death in certain patients (those critically ill, with burn injuries or with sepsis, a bacterial infection in the blood) were put in place at that time.

Likewise, as result of a third review conducted in 2018, the use of HES solutions for infusion was further restricted to only accredited hospitals, and healthcare professionals prescribing or administering the medicines had to be trained in their appropriate use. In addition, further warnings were introduced to remind healthcare professionals that these medicines must not be used in patients with sepsis or kidney impairment or in other vulnerable patients such as the critically ill in order to ensure these solutions for infusion were not used in patients who were at increased risk of harm. Market authorization holders

of HES solutions for infusion were also requested to conduct a drug utilization study to check that the restrictions were adhered to in clinical practice.

The PRAC accordingly reviewed the results of the study, which show that HES solutions for infusion are still being used outside the recommendations included in the product information and concluded that the further restrictions introduced in 2018 have not sufficiently ensured that the medicines are used safely and that HES solutions were continually used in certain groups of patients in whom serious harm has been demonstrated. In view of the serious risks that certain patient populations were still exposed to, the PRAC recommended the suspension of the marketing authorisations for HES solutions for infusion in the European Union. Accordingly, the European Commission on 24th May, 2022 issued a legal decision confirming the suspension of the market authorization of HES solution for infusion.

Healthcare professionals should be aware that treatment alternatives are available and should be selected according to relevant clinical guidelines.

Decision of PRAEC

The PRAEC after detailed deliberation and discussion and as per Rule 10 (1) (h) (v) of Pharmacovigilance Rules, 2022 decided to recommend to the Registration Board to suspend the registration of Hydroxyethyl-Starch (HES) solutions in Pakistan subject to the availability of alternative treatment options.

******************************End of Document*************************************

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: -_____

Annexure-B (SOP for PRAEC)

PROCEDURE

Method for selection of members of PRAEC.

The NPC initially screens out the experts of relevant fields having requisite qualifications & experience as per Rule 9 (3) of the Pharmacovigilance Rules, 2022. After the finalization of the experts' names, three nominations against each position are forwarded to the Authority for final approval. After approval from the Authority, the PRAEC is accordingly notified in the Official Gazette of Pakistan as per Rule 9 (1) of the Pharmacovigilance Rules, 2022 for risk management associated with the use of therapeutic goods, i.e. signal detection, causality assessment, risk minimization, communication-related to the risk of adverse events and evaluation of periodic reports etc.

Composition of PRAEC

As per Rule 9 (3) of the Pharmacovigilance Rules, 2022, the following experts are members of PRAEC, namely:

i. Chairman, PRAEC to be notified by the DRAP from the members of PRAEC for three years i.e. tenure of the committee;
ii. Director, Division of Pharmacy Services, Ex-Officio Co-Chair;
iii. Additional Director or Deputy Director, Division of Pharmacy Services, or Pharmacovigilance to be nominated by Authority who shall be its Ex-Officio Secretary;
iv. One professor of pharmacy practice to be nominated by DRAP (member);
v. Expert in basic pharmacology having at least ten-year experience to be nominated by DRAP (member);
vi. Expert of clinical pharmacology having at least ten-year experience to be nominated by DRAP(member);
vii. Expert of clinical pharmacy or clinical pharmacist having at least ten-year experience in a hospital to be notified by DRAP(member);
viii. Expert of medicine or medical specialist having at least ten-year experience in a hospital to be nominated by DRAP (member);
ix. Expert of epidemiology or pharmacoepidemiology having at least ten-year experience to be nominated by DRAP(member);
x. Expert of toxicology or forensic medicines having at least ten-year experience to be nominated by DRAP(member);
xi. Expert of pharmacovigilance at least ten-year experience in the conduct of pharmacovigilance activities to be nominated by DRAP(member);

xii. Expert of clinical trials or drug research having at least ten-year experience to be nominated by DRAP(member);

xiii. Expert of biologicals having at least ten-year experience to be nominated by DRAP(member);

xiv. Expert of biostatistics having at least ten-year experience to be nominated by DRAP(member); and

xv. As per Rule 9 (5) of the Pharmacovigilance Rules, 2022 the PRAEC may opt for experts of any speciality for a specific meeting, to assess any particular case, as and when required.

Terms of Reference (TORs) of PRAEC.

As per Rule 10 of the Pharmacovigilance Rules, 2022, the following are the function of PRAEC:

i. Cover all aspects of risk management associated with the use of therapeutic goods, i.e. signal detection, assessment, risk minimization and communication related to risks of adverse drug reactions;

ii. Perform the initial analysis and prioritization of signals which are detected and validated by NPC;

iii. Recommend to NPC to inform pharmacovigilance stakeholders through available means regarding pharmacovigilance-relevant regulatory actions such as new contraindication, a reduction in the recommended dose or a restriction to the indication of therapeutic goods etc.;

iv. Verify whether the safety concern relates to a therapeutic good or its whole class, it shall extend the scope of procedures accordingly.

v. Evaluate and assess PBRER and RMP or nominate a panel of experts or appoint a rapporteur for this purpose amongst its members or from the relevant field of expertise. The rapporteur will prepare recommendations or advice, as applicable, together with an assessment report and submit it to PRAEC.

vi. After assessment and evaluation of the database and benefit-risk assessment of confirmed signals, the PRAEC shall recommend a regulatory or necessary remedial action to the concerned Board, Committee or Division for variation, suspension, revocation, market withdrawal, change in safety specification or any other action which it considers appropriate.

vii. Recommend to the Registration Board to impose obligations on the registration holder of the therapeutic good to conduct PASS or PAES if it is found that there is a safety concern with the use of a drug;

viii. Approve nomination of a team for GVP inspection of registration holders.

ix. Shall consider or recognize and if deemed appropriate implement within Pakistan the pharmacovigilance relevant decisions of other countries and of regional and international bodies of the following nature, namely: -

a) modification or removal of an approved indication of therapeutic goods due to safety reasons;

b) addition of contraindications;

c) imposition of post-authorization safety or efficacy studies due to safety reasons;

d) major changes in the statements of warning, precaution or adverse reactions in the product information;

e) withdrawal or suspension of therapeutic goods in other countries due to safety reasons; and

f) any other safety information or decision which it considers appropriate, for ensuring the safety of the public.

Tenure of the PRAEC

As per Rule 9 (4) of the Pharmacovigilance Rules, 2022, the members of the PRAEC, other than its *Ex-Officio* members, shall hold office for three years and shall be eligible for re-nomination.

Code of conduct for the meeting of PRAEC

Conflict of interest

All the members of the PRAEC shall submit an affidavit of the non-existence of a conflict of interest at the time of their appointment in the very first meeting, in accordance with the DRAP's policy on Conflict of Interest document no ADMN/GL/CC/001, dated 15-06-2021

Meetings of PRAEC

i. As per Rule 9 (6) of the Pharmacovigilance Rules, 2022, the meetings of the PRAEC are held at such time as the committee may deem appropriate or on a quarterly basis due to the detection of risk associated with the use of therapeutic goods.

ii. The Secretary may also coordinate with the Chairman through the Co-Chair, who may at any time call a meeting if there is an important matter/emergency for its consideration.

iii. As per Rule 9 (7) of the Pharmacovigilance Rules, 2022, the meeting of PRAEC may be called within 24 hours through any means for the initial assessment of the risk and to take appropriate risk minimization measures to prevent the public from harm in case of such risks arising from the use of therapeutic goods having a major impact on the public at large or the in case of a public health emergency.

iv. The signed invitation letter for the meeting is shared with members through mailing addresses and also through available electronic means.

v. The agenda of the meeting is prepared by the Secretary, PRAEC with the support of the concerned section of NPC.

vi. Once finalized by the Secretary and Co-Chair of PRAEC, the agenda of the meeting is shared with expert members through email and a hard copy is also provided during the meeting.

vii. The meeting is chaired by the Chairman, PRAEC. However, in case of the absence of the Chairman, the Co-Chair presides over the meeting as per Rule 9 (8) of the Pharmacovigilance Rules, 2022.

viii. The quorum for holding a meeting of the PRAEC committee is one-third of its total membership as per Rule 9 (9) of the Pharmacovigilance Rules, 2022.

ix. The PRAEC decides the matter after giving opportunities to the members for their opinion and subsequent consensus reached on the matter.

x. As per Rule 10 (1) (i) of the Pharmacovigilance Rules, 2022, if consensus on scientific recommendation/ advice cannot be reached, the scientific recommendations/advice shall be adopted if supported by an absolute majority of the members of the PRAEC (i.e. favourable votes by at least half of the total members eligible to vote plus one). The members expressing divergent positions shall provide in writing, stating clearly the reasons on which they are based.

xi. The Committee reviews the progress on the recommendations given in the previous meetings for follow-up of implementation status and other necessary actions.

Minutes of Meeting

i. After the conduction of the PRAEC meeting, the minutes of the meeting are prepared by the Secretary, PRAEC with the support of each section of the NPC.

ii. After the finalization of the initial draft of the minutes by the Secretary and Co-Chair, PRAEC, the same is shared with Chairman and members for perusal and comments, if any through email.

iii. Once finalized during the email correspondence, the minutes are to be considered final and signed by the Secretary and Co-Chair, PRAEC.

iv. Necessary decisions taken during the PRAEC meeting are communicated to the concerned Board, Committee or Division or uploaded on the website as an alert or communicated to the stakeholders within 30 calendar days.

v. In the very next meeting of the PRAEC, the final minutes are confirmed and signed by all members and uploaded on the website.

Confidentiality of data

The pharmacovigilance data presented by NPC during the meeting of PRAEC such as ADRs data, RMP & PBRER, and the statistic of VigiLyze are to be considered confidential data as per section 31 of the DRAP Act, 2012 and not be shared with other people/institutions without the consent of NPC-DRAP. The purpose of the data presented during the meeting is to help and support the PRAEC for proper assessment and evaluation of the signals and to take subsequent relevant regulatory or remedial action in the matter.