MINUTES OF THE 6TH MEETING OF THE PHARMACOVIGILANCE RISK ASSESSMENT EXPERT COMMITTEE

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

File No: 17-6/2025-PRAEC(PS)

DECEMBER 31, 2025

DRUG REGULATORY AUTHORITY OF PAKISTAN

Prime Minister's National Health Complex, Park Road, Islamabad

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Minutes of the 6th meeting of the Pharmacovigilance Risk Assessment Expert Committee

The 6th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held in the Committee Room of the Drug Regulatory Authority of Pakistan (DRAP) on 31st of December 2025.

The meeting was attended by the following members:

S. No	Name	Designation
1	Prof. Dr. Moosa Khan Dean, Basic Medical Sciences and Professor & Chairman, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad	Chairman
2	Dr. Akhtar Abbas Khan, Director, Division of Pharmacy Services, DRAP.	Co-Chair
3	Mr. Abdul Mateen, Deputy Director, National Pharmacovigilance Centre, Division of Pharmacy Services, DRAP.	Secretary
4	Prof. Dr. Furqan Hashmi Professor, Pharmacy Practice, University College of Pharmacy, University of the Punjab, Lahore	Member
5	Prof. Dr. Abdul Jabbar Shah Professor & Chairperson, COMSATS University Abbottabad	Member
6	Mr. Rehan Anjum Manager Pharmacy, Shaukat Khannum Cancer Hospital and Research Centre, Peshawar	Member
7	Dr. Sajjad Ali Consultant, Internal Medicine, Shifa International Hospital, Islamabad **(attended via zoom)**	Member
8	Dr. Mohammad Imran Younus Associate Professor, Health Services Academy, Islamabad	Member
9	Dr. Samina Rehman HOD/Professor of Forensic Medicine and Toxicology, Bolan Medical College, Quetta **(attended via zoom)**	Member
10	Mst. Nazima Asghar, Clinical Pharmacy & Pharmacovigilance Officer and Hospital Pharmacist, Holy Family Hospital, Rawalpindi	Member
11	Dr. Faiza Bashir Director (Research), National Institutes of Health, Islamabad **(attended via zoom)**	Member
12	Dr. Noor-us-Saba Ex-Director of Biological Evaluation & Research Division, DRAP, Islamabad	Member
13	Dr. Farhana Badar Senior Biostatistician and Cancer Epidemiologist, Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore **(attended via zoom)**	Member

The following Officers from DRAP, Public Health Programmes (CMU) and Provincial Pharmacovigilance Centres/Provincial Health Departments also attended the 6th meeting of PRAEC-DRAP:

S. No	Name	Designation
1	Mr. Sardar Shabbir Ahmed	Secretary, PQCB, Focal Person PV, Islamabad.
2	Ms. Nusrat Rehman.	Director, Pharmacovigilance, Directorate of Drugs Control, Punjab, Lahore.
3	Dr. Seema Saifuddin	Coordinator, Common Management Unit
4	Mr. Hafiz Muhammad Ali Tayyab	Additional Director, Division of Pharmaceutical Evaluation & Registration, DRAP and Secretary, Registration Board.
5	Ms. Aqsa Hashmi	Deputy Director, National Pharmacovigilance Centre, Division of Pharmacy Services, DRAP
6	Ms. Aqsa Iftikhar	Pharmacovigilance Officer, Punjab Pharmacovigilance Centre, Directorate of Drugs Control, Punjab, Lahore.
7	Ms. Sania Nawaz Khan	Focal Person Pharmacovigilance, National TB Control Programme and National AIDS Control Programme, CMU
8	Ms. Ayesha Hameed	Focal Person Pharmacovigilance, Malaria Control Programme

Members, participants, and officers of DRAP gave their formal introductions before the start of the meeting.

Dr. Obaidullah, CEO, DRAP, welcomed the new members of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC), acknowledged their areas of expertise, and gave an opening address. He emphasised several aspects related to the importance of the Pharmacovigilance System in Pakistan.

All pharmaceutical products carry the potential for adverse effects and side effects; therefore, an early warning system for identifying rare or previously unknown adverse effects (signals), not detected during clinical trials, is essential for patient safety.

Pakistan previously lacked comprehensive reporting channels and mechanisms for collecting and analysing adverse events data, which hindered independent drug safety assessment and evidence-based regulatory decisions. Reliance on international data alone was inadequate as it did not capture risks specific to Pakistan's population and healthcare system.

Through collaborative efforts of DRAP, provincial health departments, and Public Health Programmes, an integrated nationwide mechanism for adverse event reporting has been established. This has enabled Pakistan to transition from depending solely on regulatory decisions by stringent authorities (US FDA, EMA, UK MHRA) toward independent safety assessment. The situation continues to improve through systematic provincial reporting, increasing quality and quantity of adverse event reports, and a growing national database for signal detection.

Provincial and Public Health Programme pharmacovigilance committees now conduct initial reviews within their jurisdictions and forward significant safety signals to PRAEC for national-level validation, regulatory action consideration, and coordinated risk minimisation measures.

The Committee's mandate includes evaluating safety signals, assessing causality and risk-benefit profiles, and recommending appropriate risk minimisation measures.

The World Health Organisation's Global Benchmarking Tool (GBT) serves both as an objective and a comprehensive guidance framework for national regulatory authorities. It provides specific indicators across all regulatory functions to objectively assess gaps, capacity & performance and guide strategic planning & improvement of the National Regulatory System.

The WHO Global Benchmarking audit for Pakistan's regulatory system is scheduled in the second and third quarters of 2026. The pharmacovigilance and safety monitoring function (VL) represents a critical component of this comprehensive assessment. Performance in this area will significantly impact Pakistan's overall regulatory maturity level rating.

Dr. Obaidullah expressed DRAP's high expectations from PRAEC to contribute their scientific and clinical expertise in safety-related decisions and fulfil their mandate to protect public health.

Proceedings of the Meeting formally commenced with the expression of gratitude by Professor Dr. Moosa Khan, Chairman PRAEC, to the CEO, DRAP, for the welcome remarks and comprehensive strategic vision.

Mr. Abdul Mateen, Deputy Director (NPC) and Secretary to PRAEC, presented the detailed agenda for the 6th meeting.

1. MISCELLANEOUS CASES.

1.1. Presentation about the work.

A detailed presentation on the functioning of the National Pharmacovigilance Centre (NPC) and the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was delivered by the officers of National Pharmacovigilance Centre, Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP), wherein the members were apprised of the mandate, constitution, and composition of PRAEC, the history and progress of pharmacovigilance in Pakistan following the establishment of DRAP, and the notification of Pharmacovigilance Rules, development of guidelines, conduct of capacity-building workshops, and implementation of online ADR reporting tools, along with stakeholder sensitization for adverse event reporting through designated channels; it was further

informed that the NPC is integrated with the WHO Collaborating Centre (Uppsala Monitoring Centre) and that adverse event reports collected through multiple channels are presented before PRAEC for assessment, whereupon the Committee appreciated the work of the NPC and advised further strengthening of human resources and enhanced sensitization of healthcare professionals through promotion of a no-blame culture for reporting. The committee also advised that NPC regularly submits the implementation status of its decision in future meetings.

1.2. Declaration of the non-existence of conflict of interest.

The PRAEC members were informed that the Drug Regulatory Authority of Pakistan (DRAP) has developed a Code of Conduct and 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 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 must ensure and submit an affidavit for the non-existence of professional and financial conflict of interest on the prescribed format Proforma D (Annex-A) of the aforementioned code to the DRAP in order ensure that there is no influence of any sort on the decisions of Pharmacovigilance Risk Assessment Expert Committee.

Decision:

The PRAEC members (experts) agreed to submit the signed affidavit for the non-existence of professional and financial conflict of interest as per Annex A "(Proforma-D) for expert members of Boards/Committees" to the National Pharmacovigilance Centre, DRAP.

1.3. Status of Pharmacovigilance activities in the country.

i. The Drug Regulatory Authority of Pakistan (DRAP) was established under the DRAP Act 2012, which regulates the manufacturing, import, export, storage, distribution and sale of therapeutic goods, and to bring harmony in inter-provincial trade and commerce of therapeutic goods. As per the DRAP Act, 2012, the Drug Regulatory Authority of Pakistan (DRAP) regulates therapeutic goods, which include medicines, vaccines, alternative medicines, health and OTC products, medicated cosmetics, and medical devices. Therefore,

the DRAP also has the mandate to ensure access to safe, efficacious, and quality therapeutic goods to the people of the country.

ii. As part of its mandate to ensure safety, the DRAP established the National Pharmacovigilance Centre (NPC) in 2017, which monitors the safety of therapeutic goods across the country. The Pharmacovigilance (PV) system in Pakistan under DRAP has undergone a transformative journey from a nascent concept to a structured, internationally recognised program. This momentum accelerated with Pakistan's strategic decision to join the WHO Programme for International Drug Monitoring (PIDM) in 2018, a move that integrated the country into the global pharmacovigilance community. A significant leap in regulatory maturity was achieved with the notification of the Pharmacovigilance Rules, 2022, which provided a robust legal framework, clearly delineating the responsibilities of Marketing Authorisation Holders (MAHs), Provincial Health Departments, Public Health Programs, and hospitals (both public and private), thereby moving from voluntary guidance to enforceable compliance. Under these rules, the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was notified, which is monitoring risks associated with the use of therapeutic goods. Accordingly, under these rules, DRAP developed dedicated guidelines for all pharmacovigilance stakeholders.

iii. The evolution of the system is characterised by the strategic adoption of digital tools and continuous capacity building. The subscription of VigiFlow as the National database for adverse event reporting streamlined data management and enabled seamless data sharing with the WHO's global database, VigiBase. This digital infrastructure was further expanded with the launch of the VigiMobile application and online e-reporting systems (UMC E-Forms-based) for healthcare professionals and the public, as well as the industry reporting tool for pharmaceutical companies. Parallel to technological advancement, training and capacity building of stakeholders were carried out within the available resources, conducting numerous sessions from virtual trainings during the COVID-19 pandemic for vaccines' AEFI monitoring to specialised workshops for pharmacists and public health programs, including face-to-face training sessions. Likewise, DRAP regularly issues safety alerts and Newsletters and conducts routine causality assessment and signal detection. This comprehensive approach of strengthening legal, technological, and human resource capacities has positioned the NPC as a pivotal entity in safeguarding public health by

ensuring the continuous monitoring of the safety of medicines, vaccines, and medical devices throughout the country. However, a lot has yet to be done with respect to enhancing the number of reports across the country.

iv. List of legal documents and guidelines developed by NPC-DRAP

a. The Pharmacovigilance Rules, 2022.
b. Guidelines on the National Pharmacovigilance System
c. Good Pharmacovigilance Practices for Registration Holder
d. Industry E-Reporting Manual for Registration / Marketing Authorisation Holders
e. Guidelines On Pharmacovigilance for Public Health Programmes
f. Adverse Events Reporting Guidelines for Patients, Caretakers and Consumers
g. Adverse Event Reporting Guidelines for Healthcare Professionals
h. Guidelines on Management of High Alert Medication

v. Key stakeholders of the Pharmacovigilance system in Pakistan include:

a. Drug Regulatory Authority of Pakistan (DRAP)
b. National Pharmacovigilance Centre (NPC), DRAP
c. Provincial Health Departments
d. Marketing Authorisation Holders (MAHs) – manufacturers, importers, distributors
e. Public Health Programmes (e.g. FDI/EPI, TB, HIV, Malaria programmes)
f. Public and private hospitals and healthcare institutions
g. Pharmacovigilance Risk Assessment Expert Committee (PRAEC)
h. Patients, consumers, and the public
i. Healthcare professionals (doctors, pharmacists, nurses, dentists, allied health staff)
j. Academia and research institutions

Current status of reporting from stakeholders	
Aspect	**Detail / Statistic**
Total Reports in VigiFlow (DRAP)	56,876
Reports Transferred to VigiBase (UMC)	43, 032
Pharma Companies Reports	21,447
AEFIs reports.	32,202
No of reports through E-Reporting/ Mobile App	686
Issued Safety Alerts	59
Newsletter Issued	4
Nomination of QPPVs by MAHs	160 QPPV + 20 LSO nominated

Current status of reporting from stakeholders			
Name of Province	**Provincial PV centre established in**	**Provincial PV Committee**	**No of ADRs reported**
The Punjab Centre	May-2018	2018 and 2023	1168
Islamabad	Sep-2019	May-2025	1200
Khyber Pakhtunkhwa	Sep-2024	Dec-2025	46
Azad Jammu and Kashmir	Aug-2024	April-2025	28
Gilgit Baltistan	Dec-2024	Not notified	1
Balochistan	July-2025	July-2025	15
Sindh	August-2024	August-2024	71

Number of hospitals integrated into the VigiFlow database.			
Name of Province	**Total hospitals**	**Public**	**Private**
The Punjab Centre	34	13	21
Islamabad	9	1	8
Khyber Pakhtunkhwa	20	8	12
Azad Jammu and Kashmir	12	10	2
Gilgit Baltistan	7	5	2
Balochistan	14	10	4
Sindh	15	0	15

Status of PV System in Public Health Programmes			
Name of PHP	**PV centre dated**	**PHP PV Committee**	**No ADR reports**
Federal Directorate of Immunisation	2021	2019 and 2025	32,202 AEFIs reported in COVID-19
Malaria Control Programme	Oct-2025	Oct-2025	0
TB Control Programme	Aug-2025	Aug-2025	12
HIV Control Programme	Dec-2025	Dec-2025	0

Tools for Reporting of ADRs and AEFIs	
Stakeholders	**Tool for reporting**
National Pharmacovigilance Centre	▪ Web-based Med-Vigilance E Reporting system VigiMobile Medicine ▪ Industry E reporting system for MAHs ▪ Yellow form ▪ Email and Phone number
Provincial PV Centre	▪ Reporting data to DRAP through VigiFlow ▪ For collection, Provinces have no formal reporting system except Punjab, which has the TGRP reporting forms in the Medicine Surveillance System. ▪ 111 hospitals across all provinces have been integrated into the VigiFlow
Public Health Programme	▪ Malaria and TB Control were recently integrated into the VigiFlow database. ▪ Piloting of sites for VigiFlow is being done at present

Federal Directorate of Immunisation	▪ EPI-MIS ▪ EPI-Pakistan Mobile App ▪ Hard Format Reporting from vaccination counters ▪ 1166 helpline ▪ Need to expedite reporting through VigiFlow. Integration of EPI-MIS and VigiFlow is also being explored.

Proceedings: ***The PRAEC appreciated the establishment of pharmacovigilance centres across all provinces and within public health programmes; however, it was advised to enhance awareness and the promotion of a no-blame culture among healthcare professionals to improve adverse events reporting.***

2. DOMESTIC CASES

2.1. Proposal for Revision of Registration Specifications for Injection Ceftriaxone (dry powder for injection)

i. The provincial Pharmacovigilance Centre, pursuant to the direction of the 15th meeting of the Provincial Pharmacovigilance Committee of the Punjab, held on 19-03-2025, recommended the case to the National Pharmacovigilance Centre, DRAP, Islamabad, for onward placement of the case before the Registration Board. Subsequently, the case was again submitted to NPC-DRAP by the Provincial Pharmacovigilance Centre of the Punjab, considering the decision of the 16th meeting of the Provincial Pharmacovigilance Committee of the Punjab, held on 22-09-2025. A request has also been made in this regard by the Drugs Testing Laboratory, Faisalabad, to place the case of revision of the specification of injection ceftriaxone (dry powder for injection) before the Registration Board.

ii. Provincial Pharmacovigilance Centre (PPC), Punjab had received various Therapeutic Goods Related Problem (TGRP) reports regarding Adverse Drug Reactions, including chills/shivering, headache, sweating, fever, apprehension, sweating, dyspnea, chest pain, palpitations, tachycardia and death of patients with Injection Ceftriaxone due to suspected inappropriate mixing/reconstitution practices. After due deliberation and discussion, the Provincial Pharmacovigilance Committee recommended that the DRAP reconsider the registration specifications for Injection Ceftriaxone (Dry Powder for Injection) as follows:

   a. *1-gram vial: To be registered with a minimum of 20ml of Sterile Water for Injection;*

b. *500mg & 250mg vials: To be registered with a minimum of 10ml of Sterile Water for Injection.*

c. *In addition, the vial of injection Ceftriaxone (Dry powder for Injection) may be upsized with clear 50ml demarcation to accommodate the final volume after reconstitution/dilution, ensuring suitability for direct administration to patient.*

iii. Subsequently, in its 16th meeting, along with the above-mentioned recommendations, the Punjab Provincial Pharmacovigilance Committee (PPVC), also recommended that: *DRAP may place the matter in the upcoming Registration Board meeting and accordingly the registrations of all such brands, of Injection Ceftriaxone l gram (Dry powder for Injection) supplied with 5 mL WFI for reconstitution, may be revoked with immediate effect to safeguard the public health. Any action taken in this regard may be communicated to the Directorate of Drugs Control, Punjab.*

iv. The case was discussed with the Pharmaceutical Evaluation and Registration Division (PE&R) of DRAP. It was informed that registration letters for Injection Ceftriaxone are now being issued in accordance with the Public Assessment Report of UK-MHRA, with the following information provided in the label/SmPC:

1.	Ceftriaxone 2gm Injection IV **Powder for solution for injection/infusion**	**The following condition shall appear on the label / outer carton of the product in bold and conspicuous manner:** *"Do not mix with solutions containing calcium, including Hartmann's, Ringer's and Total Parenteral Nutrition."* **With respect to the method of administration and directions for use, the following instructions should be included in the SmPC, or alternatively, any RRA-approved SmPC for Ceftriaxone 2 g Injection may be followed.** ***Intravenous injection*** *Ceftriaxone 2g powder for solution for injection or infusion should be dissolved in 20ml of Sterile WFI. The injection should be administered over at least 2 to 4 minutes directly into the vein.* ***Intravenous infusion*** *Ceftriaxone 2g powder for solution for injection or infusion should be dissolved in 40ml of one of the following calcium-free infusion solutions: Sodium chloride 0.9%, sodium chloride 0.45% and glucose 2.5%, glucose*

		5% or 10%, dextran 6% in glucose 5%, hydroxyethyl starch 6-10% infusions. The infusion should be administered immediately as a short-term infusion over at least 30 minutes.
2.	Ceftriaxone Injection 1g	i. Ceftriaxone Injection 1g (IV) should be dissolved in 10ml Water for Injection. ii. Ceftriaxone Injection 1g (IV) should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion
3.	Ceftriaxone Injection 250mg (IV)	iii. Ceftriaxone Injection 250mg (IV) shall be marketed with registered Diluent, i.e., Water for Injection 5ml. iv. Ceftriaxone Injection 250mg (IV) should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion."
4.	Ceftriaxone Injection 500mg (IV)	i. Ceftriaxone Injection 500mg (IV) shall be marketed with registered Diluent, i.e., Water for Injection 5ml. ii. Ceftriaxone Injection 500mg (IV) should be administered over at least 2 - 4 minutes, directly into the vein or via the tubing of an intravenous infusion."

Decision:

The PRAEC deliberated on the matter at length. The Pharmacovigilance (PV) Focal Person from Punjab and the Director General, Directorate of Drug Control, Punjab, Mr. Muhammad Sohail, attended the meeting via Zoom and presented a detailed explanation of the case.

The Secretary, Registration Board, Hafiz Muhammad Tayyab, informed the Committee that the Registration Board is already issuing registration letters for Ceftriaxone Injection in accordance with the Public Assessment Report of the UK-MHRA, with the relevant information duly reflected on the label and SmPC.

After due consideration, the Committee decided that the Punjab Pharmacovigilance Centre should be requested to substantiate its recommendations regarding changes in the volume of Sterile Water for Injection supplied with registered brands of Ceftriaxone (Powder for Injection 1 g, 500 mg, and 250 mg) by providing appropriate scientific and regulatory evidence at the next meeting.

2.2. Request for Review of Drug Formulation and Comparative Clinical Assessment of Inj A-Care (Atracurium) 50mg/5ml.

i. The Provincial Pharmacovigilance Centre, pursuant to the decision of the 16th meeting of the Provincial Pharmacovigilance Committee of the Punjab, held on 22-09-2025, recommended the case to DRAP. It was informed that the Committee deliberated upon the Therapeutic Goods Related Problem (TORP) report concerning the therapeutic efficacy issue reported from Benazir Bhutto Hospital, Rawalpindi, wherein it has been observed that the efficacy of Inj. A-Care (Atracurium) 50mg/5ml, Batch No. 230080, manufactured by M/s Caraway Pharmaceuticals is not up to the required standard i.e., higher doses than usual were required to achieve and maintain adequate paralysis, and the desired sedation time was only attained following multiple administrations, as compared to the standard recommended dose, indicating a potential compromise in the therapeutic efficacy of the product.

ii. Re-sampling of the concerned batch of inj. A-Care was conducted for analysis, and the said batch was declared of "Standard Quality" by the DTL Rawalpindi dated 27.03.2024. The tests performed on A-care injection by DTL Rawalpindi include Physical Test, Identification & Assay Test and Sterility test. The Committee discussed different aspects related to this case, considering various clinical and regulatory considerations, and appropriate decisions were made accordingly. In the light of aforementioned PPVC decisions, the Committee decided/recommended that a comprehensive proposal to be submitted to the Drug Regulatory Authority of Pakistan (DRAP) to review the drug formulation of said drug with the need for a comparative assessment of its pharmacological efficacy, safety profile, and therapeutic outcomes against established standard drugs, to determine its clinical relevance and continued registration. Any action taken in this regard may be communicated to the Directorate of Drugs Control, Punjab.

iii. Import data of the active pharmaceutical ingredient (API) Atracurium was reviewed to ascertain the source. Two manufacturers of Atracurium API were identified: M/s. Lianyungang Guike Pharmaceutical, China, and A Team Pharma, India. However, the latter source is only used by M/s. Caraway Pharmaceuticals in Pakistan.

Decision:

The PRAEC deliberated on the matter at length. The Pharmacovigilance (PV) Focal Person from Punjab and the Director General, Directorate of Drug Control, Punjab, Mr. Muhammad Sohail, attended the meeting via Zoom and provided a detailed presentation of the case.

The Committee was informed that the complaint pertained to a lack of efficacy of the product. However, the referred case lacked essential information, including detailed adverse event reports (lack of efficacy) of the affected patients, which is necessary to establish causality. It was noted that the Individual Case Safety Reports (ICSRs) associated with this matter may be obtained by the Punjab Pharmacovigilance Centre for a comprehensive assessment of the case series.

The Committee further decided to refer the matter to the Registration Board for appropriate regulatory action to ascertain the efficacy of A-Care manufactured by M/s Caraway Pharmaceuticals, and to prospectively consider similar issues related to other High Alert Medicines. Furthermore, the committee also recommended to the Registration Board to conduct Product Specific Inspection (PSI) of the firm, including its storage area.

2.3. Safety Signal of Renal Impairment with Entrectinib

i. Entrectinib is an Antineoplastic and Immunomodulating Agent; a protein kinase inhibitor (ATC Class L01EX)" used as a monotherapy for:

   a. Solid tumours with Nuerotrophic Tyrosine Receptor Kinase (NTRK) gene fusion in patients ≥1 month with metastatic or locally advanced cancer when surgery would cause severe harm, and not previously treated with similar NTRK inhibitors and when other treatments are unsuitable.

   b. Advanced non-small-cell lung cancer with ROS1 gene fusion in adults without prior ROS1 inhibitor therapy.

Entrectinib blocks abnormal NTRK or ROS1 fusion proteins that drive uncontrolled cancer cell proliferation, slowing tumour growth. (1, 2)

The recommended dosing is:

- Adults: 600mg once daily
- Paediatrics (>1 month to ≤6 months): 250mg/m² BSA once daily

- Duration: Until disease progression or unacceptable toxicity

For Adverse Reaction Management, temporary dose reduction, interruption, or discontinuation may be required for congestive heart failure, cognitive disorders, hyperuricemia, QT prolongation, transaminase elevation, anaemia, neutropenia, or other clinically relevant reactions.

The recommendations for use in special populations are as follows:

Hepatic impairment: No dose adjustment for mild/moderate/severe; monitor severe cases closely.

Renal impairment: No adjustment for mild/moderate; not studied in severe impairment.

Paediatric population: Paediatrics <1 month: Safety and efficacy not established.

ii. Renal impairment is reduced kidney function, affecting waste and medication removal. Many drugs require dosage adjustments or special monitoring based on kidney function estimates. A creatinine clearance of less than 90 mL/min or an eGFR of less than 90 mL/min/1.73m2 indicates this condition. (3)

Renal impairment**,** under Renal and Urinary Disorders SOC, is grouped with various primary care conditions under the HLT Renal failure and Impairment, further categorised under the HLGT Renal disorders (excluding nephropathies). Renal impairment can be acute or chronic.

Acute Kidney Injury (AKI) is a sudden loss of kidney function, often reversible with treatment.

Chronic Kidney Disease (CKD) is a gradual, irreversible loss of kidney function, usually due to underlying conditions like diabetes or high blood pressure.

End-Stage Renal Disease (ESRD) is the final stage of CKD, where kidney function is less than 15% of normal, necessitating dialysis or a kidney transplant for survival.

Kidney disease is categorised into five stages based on estimated glomerular filtration rate (eGFR), a calculation of kidney function. A normal eGFR is above 90, while the lowest is 0, indicating no remaining kidney function.

The five stages of kidney disease are:

Stage I: GFR > 90. Mild kidney damage, but normal function.

Stage II: GFR 60-89. More significant damage than stage I, but still well-functioning.

Stage III: GFR 30-59. Mild or severe loss of kidney function.

Stage IV: GFR 15-29. Severe loss of kidney function.

Stage V: GFR < 15. Kidneys nearing or at complete failure. Symptoms typically begin at this stage. (4,5)

Certain medications inhibit tubular secretion of creatinine, thereby decreasing creatinine clearance and increasing serum creatinine without a change in glomerular filtration rate (GFR). Some commonly used medications include antimicrobials, antiarrhythmic, H2 blockers, HIV treatment, PARP inhibitors, Tyrosine kinase inhibitors etc.

GFR estimates are recommended for monitoring chronic kidney disease (CKD) progression. Clinicians should not rely solely on serum creatinine monitoring to detect CKD levels and rates of progression. (6)

iii. **Case Series Assessment:** The National Pharmacovigilance Centre, during a signal detection workshop activity, identified the signal of entrectinib and renal impairment from global data. The case series comprised of 34 reports having a potential association with a positive significant value of IC_{025} and PRR, ROR more than 1.

The event renal impairment was found to be not included in the available SmPC of entrectinib by the US-FDA and EMA. However, these SmPCs do mention an increase in blood creatinine as a common ADR. Whereas SmPCs of other protein kinase inhibitors include terms relevant to kidney disorders, hinting at a class effect (analogical association). (7-10).

Entrectinib, although primarily eliminated by hepatic clearance (83%), affects the kidneys by inhibiting OCT2 and MATE1 (organic cation transporters) receptors, hence it interferes with creatinine clearance. This inhibition often leads to false creatinine-based kidney function estimates; cystatin-C measurements offer a more accurate assessment. While entrectinib-related renal impairment has been reported, the biological mechanism still mostly remains unclear. The situation other way around i.e impact of severe renal impairment on entrectinib is also unknown, and the SmPC does not suggest the need for any dose alteration in patients with renal impairment. (11-14)

Evidence and studies are lacking in pre-clinical data about renal toxicity, but some clinical data are available, which support the entrectinib-renal impairment association. Some of which also suggest hepatorenal toxicity linked to CYP450 metabolism (pharmacogenomic investigation may elucidate NTRK inhibitor renal toxicity mechanisms). (15-19).

The EMA's RMP and PBRER acquired from the MAH in Pakistan also provide supportive data in relation to the association making it an AE of special interest. (20)

Besides this the case series is lacking in some aspects, as the reported event renal impairment is a non-specific term encompassing multiple disorders and does not include symptoms with supportive diagnostic lab data (creatinine levels, cystatin C-based GFR) in the reports. Despite no evident confounding factors (concomitant nephrotoxic medications or medical history like hypertension), overall report quality was medium to poor.

In view of this assessment, the NPC concluded that the Signal may be monitored for additional evidence to strengthen the association in terms of specificity, coherence, consistency and biological plausibility.

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Discussion:

The PRAEC discussed the signal and also provided an opportunity to the MAH to give their input/comments. Ms Maryam Bano Siddiq, Patient Safety Lead, M/s Roche Pakistan Limited informed that there were currently almost no patients using entrectinib in Pakistan

and the event "Renal Impairment" is under monitoring by the company in global perspective for this adverse event and no new findings have yet been observed.

Decision: The PRAEC, after discussion and deliberation, agreed with the proposal of the NPC submitted as per Rule 4 (1) (viii), to continue monitoring the signal and accordingly inform the MAH for the following:

i. ***Improvement of ADR reports submitted to NPC to capture maximum information.***
ii. ***Awareness for healthcare professionals to monitor Cystatin C GFR lab findings in addition to creatine clearance when entrectinib is used in their prospective enrolled patients.***
iii. ***Awareness of HCPs to actively and thoroughly monitor and report any events with entrectinib.***

2.4. Safety Signal of Myocardial Infarction with Pertuzumab

i. **Pertuzumab** is an HER2 (Human Epidermal Growth Factor Receptor 2) inhibitor and neu receptor antagonist (L01FD). It is a humanised IgG1 monoclonal antibody indicated for the treatment of HER2-positive early or metastatic breast cancer. It is used as an intravenous infusion in combination with trastuzumab and docetaxel in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease. The initial dose is 840 mg followed every three weeks thereafter by 420 mg.

ii. **Myocardial infarction** is classified as either an Ischemic coronary artery disorder under the Cardiac disorders SOC or as a coronary necrosis and vascular insufficiency under the Vascular disorders SOC. It typically results from an imbalance in oxygen supply and demand, often due to an acute reduction in blood supply to a portion of the myocardium. While the clinical presentation of a patient is a key component in the overall evaluation of a patient with myocardial infarction, many events are either silent or not clinically recognised by patients' families and healthcare providers. The lack of oxygen causes cells to die (necrosis), starting from the inner layer, leading to impaired heart function, inflammation, scar formation and remodeling ultimately causing heart failure if severe.

iii. **Case Series Assessment:** The National Pharmacovigilance Centre, through a regular signal detection activity, identified the drug event combination of Pertuzumab and Myocardial Infarction (MI). The event MI is not listed in the SmPCs of the drug from the US-FDA and EMA, supported with significant positive IC_{025} value.

The case series comprised of four serious reports, which reported the standard concomitant treatment with trastuzumab, besides which no other medication or medical history was available.

The signal was validated with information regarding cardiotoxicity (LVEF and CHF) in the SmPCs of pertuzumab and trastuzumab under cardiac disorders in the ADRs section. Left Ventricular Function or decrease Left Ventricular Ejection Fraction (LVEF) is reported with medicinal products blocking HER2 activity and recent MI can also impair LVEF. The SmPC of rituximab (A monoclonal antibody L01FA CD20 receptor inhibitor), mentions MI as a common ADR in clinical trials data and warnings section as an infusion related reaction. But this analogy is weak due to difference in receptor binding activity. (1-4)

The biological mechanism/ plausibility linking pertuzumab to myocardial infarction remains unclear. Pertuzumab inhibits HER receptors signaling which is essential for survival and repair of cardiomyocytes causing cellular dysfunction, apoptosis and mitochondrial damage, primarily manifesting as heart failure/LVEF dysfunction rather than ischemic events. Myocardial infarction typically results from atherosclerotic blockage or thrombosis, distinct from pertuzumab's cardiotoxic mechanism. (5)

Literature and clinical research on cardiotoxicity in relation to pertuzumab is limited, with many trials either ongoing or unpublished. While myocardial infarction can lead to heart failure through scarred myocardium, evidence is conflicting as one study suggests no association between MI and HER2 inhibition, while another links cardiotoxicity to HER2 therapy. Further research is needed to clarify the clinical spectrum and mechanisms of pertuzumab-related myocardial infarction. (6-13)

In view of this assessment the National Pharmacovigilance Centre concluded that the Signal needs monitoring for accumulation of more reports, literature evidence and publication of results ongoing clinical trials.

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Discussion:

The PRAEC discussed the signal and also provided an opportunity to the MAH to give their input/comments. Ms Maryam Bano Siddiq, Patient Safety Lead, M/s Roche Pakistan Limited, informed that pertuzumab is always used with trastuzumab and before pertuzumab's use, cardiac risk is required to be considered with concomitant use of anthracyclines.

Decision:

The PRAEC, after discussion and deliberation, agreed with the proposal of the NPC to continue monitoring the signal.

3. RELIANCE ON INTERNATIONAL SAFETY DECISIONS.

i. Stringent medicines regulatory authorities such as the United States Food and Drug Administration (US-FDA), the European Medicines Agency (EMA), and the Medicines and Healthcare Products Regulatory Agency (MHRA), United Kingdom, regularly monitor the safety of medicines through the collection of adverse events data using both spontaneous and active surveillance systems. Based on detected safety signals, followed by scientific evaluation and benefit–risk assessment, these authorities undertake appropriate regulatory actions to ensure the continued safety of medicines available in their respective markets.

ii. The National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP), routinely reviews safety alerts and information issued by stringent medicines regulatory authorities. Where deemed appropriate, such cases are presented before the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of DRAP for reliance on international regulatory information. Upon approval by the Committee, the necessary risk minimisation measures are recommended to the Registration Board for implementation in Pakistan.

iii. Rule 10 (1) (h) of the Pharmacovigilance Rules, 2022 is related to reliance on Pharmacovigilance decisions in Pakistan. The said rule is reproduced as under:

"The PRAEC shall consider or recognise 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 a therapeutic good due to safety reasons;

(ii) addition of contraindications;

(iii) imposition of post-authorisation 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."*

iv. Previously, the reference regulatory authorities for reliance purposes were not identified for pharmacovigilance. Accordingly, the Pharmacovigilance Risk Assessment Expert Committee (PRAEC), in its 2nd meeting held on 7th of March, 2023 adopted a list (Annexe-B) of reference regulatory authorities, as well as regional and international bodies, for reliance on pharmacovigilance-related regulatory decisions taken in accordance with Rule 10(1)(h) of the Pharmacovigilance Rules, 2022, in Pakistan.

v. Therefore, regulatory decisions issued by the reference regulatory authorities are hereby submitted for consideration of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) for advisory recommendations in the following cases:

3.1 Isotretinoin: Sacroiliitis

i. The Health Canada, through its Newsletter Infowatch (March 2025) informed about assessing the potential risk of Sacroiliitis with Isotretinoin. The safety review found a possible link between isotretinoin and the risk of sacroiliitis. It was informed that Health Canada will work with the manufacturers to update the product safety information in the Canadian product monograph (CPM) for isotretinoin-containing products to include the risk. Sacroiliitis, inflammation of the sacroiliac joints (where the spine connects to the pelvis), usually results in pain.

ii. Isotretinoin is a prescription for the treatment of severe forms of acne in patients 12 years of age and older, which is used when the acne fails to respond to other treatments.

iii. Health Canada reviewed 24 international cases of sacroiliitis in patients taking isotretinoin. Of those 24 cases, 23 were found to be possibly linked to the use of isotretinoin, and 1 was unlikely to be linked. The average age was 20 years in cases where the age was provided. No deaths were reported among the 24 cases reviewed.

iv. Health Canada also reviewed 18 articles published in the scientific literature. While the studies supported a link between the risk of sacroiliitis and the use of isotretinoin, they did not identify a clear biological mechanism to explain how isotretinoin use could lead to sacroiliitis. In both the cases reviewed and the scientific literature, sacroiliitis improved after discontinuation of isotretinoin and appropriate treatment.

Decision: The PRAEC decided as follows: -

a. ***As per Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, registration holders of isotretinoin-containing medicines are required to include information on the risk of sacroiliitis in the Adverse Drug Reactions and Warnings and Precautions sections of the SmPC/label, in line with the Health Canada Product Monograph; and***

b. ***The PRAEC, as per Rule 10(1)(e) recommended to the Registration Board to direct all registration holders of isotretinoin-containing medicines to update the prescribing information in light of the decisions of Health Canada and PRAEC-DRAP.***

3.2 Mesalazine: Risk of idiopathic intracranial hypertension

i. The HPRA of Ireland, through a Drug Safety Newsletter in June, 2025, announced that the product information for mesalazine is updated to include the risk of idiopathic intracranial hypertension (pseudotumor cerebri).

ii. Mesalazine (5-aminosalicylic acid) is an intestinal anti-inflammatory agent indicated for the treatment of mild to moderate ulcerative colitis, both in the acute phase and in the prevention of recurrence, treatment of Crohn's disease, both in the acute (active) phase and for the prevention of recurrence, as long as the disease is restricted to the colon.

iii. The EMA's PRAC recommendations are based on a review of available data on benign intracranial hypertension from the literature and spontaneous reports, including, in some cases, a close temporal relationship, a positive de-challenge and/or re-challenge. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.

iv. The MHRA-UK on 4th of December 2025, through a Drug Safety Update, also informed that idiopathic intracranial hypertension (IIH) has been very rarely reported in patients treated with mesalazine. Following a recent review, warnings for idiopathic intracranial hypertension are being added to the product information for all mesalazine products.

v. The recent European review of safety data for mesalazine identified an association between mesalazine and idiopathic intracranial hypertension following very rare reports of this event. Consequently, recommendations have been made to update the product information for mesalazine products to contain warnings for idiopathic intracranial hypertension. The benefit-risk balance remains unchanged in the approved indications.

vi. The findings of this review were considered by the UK's independent Pharmacovigilance Expert Advisory Committee (PEAG) of the Commission on Human Medicines (CHM), which agreed with the recommendations and advised that the MHRA inform healthcare professionals and patients of the possibility of idiopathic intracranial hypertension with mesalazine.

vii. The number of reports of intracranial hypertension and mesalazine received in the UK and identified through the European review is very low. The MHRA has received 6 UK Yellow Card reports of increased intracranial pressure disorders associated with mesalazine

viii. It was advised that prior to prescribing, healthcare professionals should warn patients of signs and symptoms of idiopathic intracranial hypertension. Patients should be advised to tell their doctor immediately if they experience symptoms, including progressively more severe and recurrent headache, disturbed vision, ringing or buzzing in the ears, back pain, dizziness, or neck pain, as these could be symptoms of IIH. Additionally, caution is advised when prescribing for patients who have previously diagnosed or suspected idiopathic intracranial hypertension. If idiopathic intracranial hypertension occurs, discontinuation of mesalazine should be considered.

Decision: The PRAEC decided as follows: -

a. ***As per Rule 10 (1)(h) (iv) of the Pharmacovigilance Rules, 2022, registration holders are required to include information regarding the risk of idiopathic intracranial hypertension in the Warnings and Precautions section and also list this risk with a frequency of "not known" in the Adverse Drug Reactions (ADRs) section of the SmPC/label for all mesalazine-containing medicine in Pakistan in line with MHRA-UK decision; and***

b. ***The PRAEC, as per Rule 10(1)(e) of the Pharmacovigilance Rules, 2022, recommended to the Registration Board to direct all registration holders of mesalazine-containing medicines to update the SmPC/label in light of the decisions of MHRA-UK and PRAEC-DRAP.***

3.3 Thiopurines: Intrahepatic cholestasis of pregnancy

i. The MHRA on 15th of May, 2025, through a Drug Safety Update informed that Intrahepatic cholestasis of pregnancy (ICP) has been rarely reported in patients treated with azathioprine products and is believed to be a risk applicable to all drugs in the thiopurine class (azathioprine, mercaptopurine and tioguanine). Cholestasis of pregnancy associated with thiopurines tends to occur earlier in pregnancy than non-drug-induced cholestasis of pregnancy, and elevated bile acid levels may not be reduced with ursodeoxycholic acid.

ii. The thiopurines include azathioprine, 6-Mercaptopurine and thioguanine (also known as tioguanine). Their uses are in anticancer indications, primarily leukaemia, and immunosuppression to treat inflammatory disorders such as inflammatory bowel diseases (IBD) and to increase graft survival following organ transplant.

iii. A risk of developing intrahepatic cholestasis of pregnancy (ICP) has been identified from a small number of case reports in the scientific literature. ICP has been reported in some pregnant patients treated with azathioprine and mercaptopurine, and, due to similar metabolic pathways utilised by thiopurines, this risk is believed to be applicable to all drugs in the thiopurine class (azathioprine, mercaptopurine and tioguanine). For context, the occurrence of thiopurine-induced ICP is thought to occur much less frequently than non-thiopurine-induced ICP, which occurs in roughly 1 in every 150 pregnancies.

iv. Case reports occur mainly in patients being treated for IBD or in transplant recipients. In many cases, ICP associated with thiopurine treatment has developed earlier in pregnancy than typical non-drug-induced ICP, and in some cases, bile acid levels did not reduce with ursodeoxycholic acid. However, in some cases, improvement in bile acid and liver function did occur on stopping thiopurine. Reported cases were often serious, with some resulting in fetal death. However, reporting bias may result in the more serious cases being reported.

v. Early diagnosis and discontinuation or dose reduction of the thiopurine may minimise adverse effects on the fetus. A thorough assessment of the important benefits of treatment of the underlying disease against the risk of thiopurines to the mother and the effects of ICP on the fetus should be performed if ICP is confirmed.

vi. In patients with ICP, measure serum bile acids to identify pregnancies at particular risk of spontaneous preterm birth (≥40uM) or stillbirth (non-fasting serum bile acids ≥100uM).

vii. Patients should be made aware of the signs and symptoms of ICP, which include intense itching without a rash, nausea, and loss of appetite, and advised to seek healthcare professional advice immediately if they experience these symptoms.

viii. The Saudi Food & Drug Authority (SFDA) on 13-06-2025, through a safety communication, announced that the product information for thiopurines, including

azathioprine and mercaptopurine, will be updated to include the potential risk of intrahepatic cholestasis of pregnancy (ICP). ICP, also known as obstetric cholestasis, is a liver disorder that occurs during pregnancy, characterised by intense itching and elevated bile acid levels. It was informed that globally, post-marketing cases of ICP have been reported in women treated with thiopurine drugs for Crohn's disease (CD) or ulcerative colitis (UC)] or systemic lupus erythematosus (SLE) during pregnancy, based on which SFDA took the decision.

ix. Azathioprine is indicated for the treatment of inflammatory bowel disease and rheumatoid arthritis, and mercaptopurine is for acute lymphoblastic leukaemia (ALL). Thiopurines have already been labelled for the risk of hepatotoxicity and foetal harm with use during pregnancy, and should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risks versus benefits.

x. The SFDA advises healthcare professionals to closely monitor pregnant patients using thiopurines and educate patients to seek medical help if they develop signs and symptoms of ICP, such as itching, dark urine and pale stools.

Decision: The PRAEC decided as follows: -

a. ***As per Rule 10 (1) (h) (iv) of the Pharmacovigilance Rules, 2022, registration holders are required to include the risk of intrahepatic cholestasis of pregnancy, with a frequency of "not known", in the Adverse Drug Reactions and Warnings and Precautions sections of the SmPC/label of thiopurine-containing medicines registered in Pakistan, in line with the SmPC approved by MHRA; and***

b. ***The PRAEC, as per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022, recommended to the Registration Board to direct all registration holders of thiopurine-containing medicines to update the SmPC/label in light of the decisions of MHRA-UK and PRAEC-DRAP.***

3.4 Finasteride, Dutasteride: Potential risk of suicidal thoughts

i. The PRAC of the EMA in its meeting of 5th -8th of May, 2025, concluded its review of the following referral by France. The PRAC reviewed the available data in relation to suicidal

ideation and behaviours associated with the use of finasteride- and dutasteride-containing products. The data included the responses submitted by the MAHs in writing, data from clinical trials, spontaneous reporting and literature, non-clinical data, as well as interventions by third parties.

ii. Based on the evaluated cases of suicidal ideation or suicidal behaviours reported with oral finasteride, PRAC confirmed a causal association between oral finasteride and suicidal ideation. Therefore, suicidal ideation should be reflected as an undesirable effect in the product information of all medicinal products containing finasteride 1 mg or finasteride 5 mg for oral use, with a frequency 'not known'. PRAC noted that the product information of all medicinal products containing finasteride 1 mg or finasteride 5 mg for oral use already includes a warning on mood alterations, including suicidal ideation. PRAC also concluded that sexual dysfunction, a known adverse drug reaction of finasteride, may have a contributory role in suicidal ideation in some patients being treated with finasteride 1 mg for oral use and recommended that this to be reflected as a warning in the product information of these products.

iii. The product information for finasteride 1 mg *will now also alert patients* about the need to seek medical advice if they experience problems with sexual function that have been reported to contribute to mood alterations and suicidal ideation in some patients. *A patient card* will be included in the 1 mg finasteride package to remind patients of these risks and to advise them about the appropriate course of action.

iv. Regarding finasteride-containing medicinal products for cutaneous use, PRAC did not identify sufficient evidence linking suicidal ideation to such products that would prompt an update of the existing warning on mood alterations. Thus, PRAC considered that the benefit-risk balance of medicinal products containing finasteride for cutaneous use remains favourable and recommended the maintenance of their marketing authorisations.

v. The PRAC confirmed that suicidal ideation (suicidal thoughts) as an adverse reaction of finasteride tablets, but concluded that the benefits of finasteride and dutasteride medicines continue to outweigh their risks for all approved uses. The frequency of the adverse reaction is unknown.

vi. Finasteride (oral 1 mg tablet and skin solution) is used to treat the early stages of androgenic alopecia in men aged 18 to 41 years. Finasteride (oral 5 mg tablet) and dutasteride (0.5 mg capsules) are used to treat men with benign prostatic hyperplasia (BPH). Most cases of suicidal ideation were reported in people using 1 mg finasteride to treat hair loss due to male hormones.

vii. Although a link between suicidal ideation and dutasteride was not established based on the reviewed data, dutasteride works in the same way as finasteride. Therefore, information about the mood changes seen with finasteride will also be added to dutasteride's product information as a precaution

viii. The case was previously discussed in the 2nd meeting of PRAEC-DRAP held on 7th March, 2023, as per the decision of the Health Sciences Authority (HSA) of Singapore and Health Canada. 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.

Decision: The PRAEC decided as follows: -

a. ***As per Rule 10 (1)(h) (iv) of the Pharmacovigilance Rules, 2022, registration holders are required to include the risk of suicidal ideation (suicidal thoughts) in the Adverse Drug Reactions section, with a frequency of "unknown", for oral finasteride and dutasteride-containing medicines registered in Pakistan, in line with the decision of EMA-PRAC; and***

b. ***The PRAEC as per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022, recommended to the Registration Board to direct all registration holders of oral Finasteride and dutasteride-containing medicines to update the SmPC/label in light of the decisions of EMA-PRAC and PRAEC-DRAP.***

3.5 Sulfamethoxazole, trimethoprim: Risk of circulatory shock

i. The PRAC of the EMA in its meeting of 5-8th of May, 2025, recommended updating the product information for combination products of sulfamethoxazole and trimethoprim (also called *cotrimoxazole*) to include the risk of circulatory shock. The PRAC recommended

that under the undesirable effects section of the Summary of Product Characteristics (SmPC), drug reaction of "Circulatory shock" will be added with the frequency "Not known".

ii. It was also informed that cases of circulatory shock, often accompanied by fever and not responding to standard treatment for hypersensitivity, have been reported with the medicine, mainly in immunocompromised patients. Patients should call the emergency department immediately if experiencing multiple symptoms such as fever, very low blood pressure or increased heart rate after taking this drug, as it may be a sign of shock.

iii. A combination of sulfamethoxazole and trimethoprim is a prescription antibiotic medicine indicated for the treatment of various bacterial infections.

Decision: The PRAEC decided as follows: -

a. ***As per Rule 10 (1)(h) (iv) of the Pharmacovigilance Rules, 2022, registration holders are required to include the risk of "circulatory shock", with a frequency of "not-known", in the Adverse Drug Reactions (ADRs) section of the SmPC/label of the sulfamethoxazole–trimethoprim combination, in line with the decision of EMA-PRAC; and***

b. ***The PRAEC, as per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022, recommended to the Registration Board to direct all registration holders of drugs containing sulfamethoxazole and trimethoprim drug combination to update the SmPC/label in light of the decisions of EMA-PRAC and PRAEC-DRAP.***

3.6 Semaglutide: Risk of non-arteritic anterior ischemic optic neuropathy (NAION)

i. The PRAC of the EMA on 6th of June, 2025, announced that it has concluded its review of medicines containing semaglutide following concerns regarding a possible increased risk of developing non-arteritic anterior ischemic optic neuropathy (NAION). Accordingly, the PRAC recommended updating the product information for semaglutide (Ozempic®, Rybelsus® and Wegovy®) to include the risk of non-arteritic anterior ischemic optic neuropathy (NAION) with a frequency of 'very rare', (meaning it may affect up to 1 in 10,000 people taking semaglutide). NAION is an eye condition that may cause loss of vision.

ii. Results from several large epidemiological studies (for example, article 1 and article 2) suggest that exposure to semaglutide in adults with type 2 diabetes is associated with an approximately two-fold increase in the risk of developing NAION compared with people not taking the medicine. This corresponds to approximately one additional case of NAION per 10,000 person-years of treatment. Data from clinical trials also point to a slightly higher risk of developing the condition in people taking semaglutide, compared with people taking a placebo.

iii. If patients experience a sudden loss of vision or rapidly worsening eyesight during treatment with semaglutide, they should contact their doctor without delay. If NAION is confirmed, treatment with semaglutide should be stopped.

iv. Semaglutide is a GLP-1 (glucagon-like peptide-1) receptor agonist and is indicated for the treatment of diabetes and obesity. Semaglutide acts in the same way as GLP-1 (a natural hormone in the body) by increasing the amount of insulin that the pancreas releases in response to food. This helps with the control of blood glucose levels. Semaglutide also regulates appetite by increasing a person's feelings of fullness, while reducing their food intake, hunger and cravings.

v. Subsequently, the WHO on 27th of June 2025, has also issued an alert to healthcare professionals and regulatory authorities about the risk of non-arteritic anterior ischemic optic neuropathy (NAION) associated with the use of semaglutide medicines, following the recommendation by EMA-PRAC. At its May 2025 meeting, the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) also evaluated the evidence and concluded that the Risk Management Plan for semaglutide should be revised to include NAION as a potential risk, including any required additional pharmacovigilance activities. WHO is issuing this safety alert due to the widespread global use of semaglutide and the serious nature of NAION. Furthermore, the WHO has received individual case safety reports (ICSRs) of NAION following semaglutide administration from multiple countries through VigiBase, the global database of reported adverse events of medicinal products.

Decision: The PRAEC decided as follows: -

a. ***As per Rule 10 (1)(h) (iv) of the Pharmacovigilance Rules, 2022, registration holders are required to include the risk of non-arteritic anterior ischemic optic neuropathy (NAION) in the Warnings and Precautions section and list it with a frequency of "very rare" in the Adverse Drug Reactions (ADRs) section of the SmPC/label of semaglutide-containing medicines registered in Pakistan, in line with the decisions of EMA-PRAC and WHO; and***

b. ***The PRAEC as per Rule 10 (1) (e) of the Pharmacovigilance Rules, 2022, recommended to the Registration Board to direct all registration holders of drugs containing Semaglutide to update the SmPC/label in light of the decisions of EMA-PRAC, WHO and PRAEC-DRAP.***

3.7 Cetirizine, levocetirizine: Risk of severe itching after discontinuation of long-term use

i. The US Food and Drug Administration (FDA) in May 2025 warned about the risk of severe itching after discontinuation of long-term use of allergy medicines (Cetirizine and levocetirizine). FDA warned that patients stopping the oral allergy medicines cetirizine (Zyrtec®) or levocetirizine (Xyzal®) after long-term use may experience rare but severe itching, also called pruritus.

ii. Cetirizine and levocetirizine are antihistamines and are approved to treat seasonal allergies, available in prescription and over-the-counter (OTC) forms. Cetirizine and levocetirizine are antihistamines that block a molecule called histamine that the body releases during allergic reactions. Both medicines are approved to treat seasonal allergies, called seasonal allergic rhinitis, in adults and children 2 years and older. The medicines are also approved to treat year-round allergies, called perennial allergic rhinitis, and chronic hives, called chronic idiopathic urticaria, in patients 6 months and older.

iii. The itching has been reported in patients who used these medicines daily, typically for at least a few months and often for years. Patients did not experience itching before starting the medicines. Reported cases were rare but sometimes serious, with patients experiencing widespread, severe itching that required medical intervention.

iv. Patients were advised to contact their healthcare professional if they develop severe itching after stopping cetirizine or levocetirizine. Itching typically occurred within a few days of stopping these medicines after daily use for a few months to years. Healthcare professionals

were advised to discuss the risk of pruritus after stopping cetirizine or levocetirizine with patients when prescribing or recommending these medicines, especially if planned for chronic use, and with those who indicate they are using OTC versions

Decision: ***The PRAEC, in accordance with Rule 10(1)(b) and Rule 10(1)(h)(vi) of the Pharmacovigilance Rules, 2022, decided to recommend that the National Pharmacovigilance Centre issue a safety alert to inform healthcare professionals and patients, warning them of the risk of severe pruritus following discontinuation of long-term use of allergy medicines, namely cetirizine and levocetirizine, in line with the decision of the US FDA.***

ANNEX A:

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

AFFIDAVIT FOR NON-EXISTENCE 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