DRUG REGULATORY AUTHORITY OF PAKISTAN
NATIONAL PHARMACOVIGILANCE CENTRE

PHARMACOVIGILANCE NEWSLETTER

Issue No: 01 | May-2025 | Volume: 03

Industry e-Reporting System

In order to promote transparency and to ease the submission of individual case safety reports (ICSRs), the Drug Regulatory Authority of Pakistan (DRAP), in collaboration with the Uppsala Monitoring Centre (UMC), Sweden, has launched an Industry e-reporting system. This system is a one-way submission tool, where the pharmaceutical companies directly submit the reports to the National Pharmacovigilance Centre (NPC) through two modules, namely: E2B XML submission and manual data entry, along with features of auto-acknowledgement and follow-up submission of ICSRs. The system was initially started in a pilot group of pharmaceutical companies. Later on, the e-reporting system was extended to all pharmaceutical companies across Pakistan through an official notification. The DRAP provides secure logins to two nominated officers of pharmaceutical companies, preferably a Qualified Person for Pharmacovigilance (QPPV)/Local Safety officer and a backup person. DRAP has also developed an industry e-reporting manual for guidance of the pharma industry, which is available on the official website. The system is in place, and most of the ICSRs from pharmaceutical companies are now submitted through this platform.

Promoting "No Blame Culture" Enhancing Pharmacovigilance in Pakistan

Pharmacovigilance is the cornerstone of drug safety in Pakistan, ensuring the continued effectiveness and reliability of medications. Reporting adverse drug reactions (ADRs) and medication errors is not merely a regulatory requirement but a moral imperative to safeguard patient well-being. However, underreporting continues to be a prevalent issue, often stemming from apprehension regarding blame or professional consequences. At DRAP, we are resolute in our commitment to fostering a "no-blame culture"—an environment that prioritises transparency, continuous learning, and collective responsibility.

The Significance of "No-Blame Culture" in Healthcare

1. Prompt Action Saves Lives:

Timely reporting facilitates swift action, ranging from updating drug labels to restricting potentially hazardous medications. Prompt reporting and actions avert potential harm. Your vigilance can have a profound impact on patients' lives.

2. Enhancing Systemic Safety:

Errors often originate from systemic deficiencies rather than individual shortcomings. By focusing on the underlying causes of incidents rather than assigning blame, we can redesign processes to prevent recurrence. A nurse's timely reporting on a dosing error can trigger hospital-wide training on prescription protocols.

3. Empowering Collective Responsibility:

Pharmacovigilance is not solely the responsibility of Physicians; other healthcare professionals, such as Pharmacists, Nurses and even patients, play pivotal roles in ensuring drug safety. A culture that promotes accountability and values everyone's perspectives can strengthen Pakistan's drug safety framework.

"Together, We Protect Pakistan's Health

Silence is the greatest risk to Patient Safety. By embracing a no-blame culture, we transform fear into courage and errors into progress. Every report you submit fortifies our healthcare system, ensuring safer treatments for millions."

Report Today. Safeguard Tomorrow.

Dr. Obaidullah
CEO-DRAP

Breaking Barriers: How DRAP Supports You-

We acknowledge the challenges you encounter:

Fear of Retaliation: "Will reporting jeopardise professional standing?"

Lack of Clarity: "How to initiate the reporting process?"

Doubt about Impact: "Will a report have a meaningful effect?"

Here's how we address these concerns:

Reporters' identity remains protected, utilise DRAP tools such as VigiMobile or the Med-E Vigilance reporting system to submit adverse drug reaction (ADR) reports confidentially.

Streamlined Reporting Process:

Reporting forms require less than five minutes to complete. Refer to our guidelines to learn about how to report.

You can contribute to building a "No-Blame Culture" in the country.

Proactive Reporting:

Identify any unusual patient reactions and promptly report them. Utilise DRAP's tools like VigiMobile and/or Med-Vigilance E-reporting system or VigiFlow account.

Encourage colleagues who speak up. Share success stories in hospital meetings or share with us via DRAP's newsletter.

Advocate for systemic change by identifying process gaps in your institute.

DRAP's Commitment to You

We focus on fixing systems by root cause analysis, not assigning blame. Outstanding reporters will be acknowledged by DRAP in it's Newsletter.

Antimicrobial Use in Pakistan: 2023 GLASS Report Highlights and Pathways for Smarter Stewardship

Data submitted by Pakistan to the World Health Organisation's Global Antimicrobial Resistance and Use Surveillance System (GLASS) provides a critical snapshot of antimicrobial consumption across the country in 2023.

The data was acquired from the Provinces of Punjab, Khyber Pakhtunkhwa, Balochistan, Sindh, Islamabad Capital Territory, Gilgit Baltistan and Azad Jammu &Kashmir.

With 71% of public sector procurement captured from hospitals across all provinces and administrative territories, the dataset reflects substantial National public sector coverage and offers valuable insights into usage patterns, and how we can enhance them.

Key Findings from 2023

- **Overall Antibacterial Use:** Antibacterial consumption according to the reported data was 2.17 Defined Daily Doses (DDD) per 1,000 inhabitants per day in 2023. This number indicates a small fraction of antimicrobials used by the public sector.
- **Dominant Antibacterial Classes:**
  - Beta-lactam antibacterials (excluding penicillins) were the most consumed (29.3% of total), followed by sulfonamides and trimethoprim (18.2%) and quinolones (18.0%).
  - Route of Administration: Oral antimicrobials represented 89.5% of total use, with parenteral forms making up just 10.5%.
- **AWaRe Distribution:**
  - Access antibiotics: 44.5% (below WHO's target of ⩾60%)
  - Watch antibiotics: 55.1%
  - Reserve antibiotics: 0.08%

This indicates an ongoing reliance on Watch-category antibiotics, which carry a higher risk of fostering resistance.

Spotlight on Frequently Used Antimicrobials

- **Oral Agents:** Cefixime, sulfamethoxazole-trimethoprim, and amoxicillin dominated usage.
- **Parenteral Agents:** Ceftriaxone was the leading injectable, making up 69% of DU75 consumption in this category, which indicates that Ceftriaxone leading injectable.

Recommendations for Smarter Antimicrobial Procurement and Use

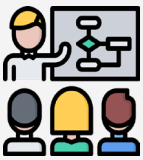
To curb the risk of antimicrobial resistance and align with WHO stewardship goals, several strategic shifts are essential:

1. **Procurement Policies Based on AWaRe Classification**
   - Prioritise Access-group antibiotics in public procurement frameworks.
   - Introduce quotas or tenders that favour Access antibiotics unless clinical need justifies Watch or Reserve options.
   - Reserve-category agents should only be stocked in tertiary care or specialised infectious disease centres under stewardship oversight.

2. **Integrated National Antimicrobial Stewardship Programs (ASPs)**
   - Embed ASPs in both public and private hospital settings, with periodic audits of prescription practices.
   - Promote standardised treatment guidelines anchored in the AWaRe framework.
3. **Capacity Building**
   - Strengthen training for physicians, pharmacists, nurses and paramedics on the rational use of antimicrobials.
   - Disseminate updated clinical guidelines incorporating microbiological surveillance data (antibiograms).
4. **Public Awareness and Community Engagement**
   - Launch targeted awareness campaigns about the risks of antibiotic overuse.
   - Empower patients to question non-essential prescriptions and promote adherence to prescribed treatments.

While Pakistan's 2023 antimicrobial consumption reporting marks a commendable step forward in transparency and surveillance, it underscores an urgent need to recalibrate public procurement and prescribing behaviour. Aligning antimicrobial use with the WHO's AWaRe classification not only safeguards future treatment efficacy but is vital to curbing the tide of antimicrobial resistance regionally and globally.

5th Meeting of Pharmacovigilance Risk Assessment Expert Committee (PRAEC)



The 5th meeting of PRAEC was held on the 2nd of January, 2025, in the Drug Regulatory Authority of Pakistan (DRAP) at its Islamabad headquarters. The meeting was chaired by Brig Ritd. Dr. Akbar Waheed, Professor of Pharmacology, Islamic International Medical College, Islamabad and Co-Chaired By Abdullah Diyo, Head of the National Pharmacovigilance Centre (NPC) / Director, Division of Pharmacy Services. Abdul Mateen, Deputy Director, Pharmacovigilance, was the Secretary of the meeting.

Key discussions centred on implementing the Pharmacovigilance Rules, 2022, and the World Health Organisation's (WHO) Institutional Development Plans (IDPs) aimed at achieving World Listed Authority (WLA) Level 3 status. Progress was noted in Punjab, Islamabad, Khyber Pakhtunkhwa, and Azad Jammu & Kashmir, with the establishment of pharmacovigilance centres and integration of 39 hospitals into the VigiFlow database. However, challenges persist in Balochistan and Sindh, where Pharmacovigilnace centres and committees remain unnotified. Recommendations included appointing dedicated pharmacovigilance officers (at least one per 200 hospital beds), establishing hospital-level pharmacovigilance committees, and extending VigiFlow access to private hospitals. DRAP was tasked with coordinating these initiatives and enhancing training programs.

A significant safety concern discussed involved patient deaths linked to the unintentional mixing of high-alert medications during the reconstitution of injection Ceftriaxone in a hospital. The case was recommended by the Provincial Pharmacovigilance Centre of the Punjab. The PRAEC, after deliberation, recommended to the Registration Board that injection Potassium Chloride also be supplied in ready-to-use, pre-diluted forms. The Registration Board was advised to take necessary regulatory actions in this regard.

Capacity Building of Stakeholders

To adopt a harmonised adverse drug reaction (ADR) reporting system across the country, the Drug Regulatory Authority of Pakistan (DRAP) initiated active coordination with Provincial Health Departments for the integration of hospitals into the VigiFlow database. As a result, 39 hospitals from the Punjab, Islamabad, Khyber Pakhtunkhwa, Azad Jammu and Kashmir, and Gilgit Baltistan have been integrated into the National database. Necessary training on VigiFlow data entry and coding was provided to all nominated officers from these hospitals during August and September 2024.

Similarly, the National Pharmacovigilance Centre (NPC), DRAP, conducted a series of online training sessions for registration holders (manufacturers and importers) of therapeutic goods. In a first-of-its-kind initiative, DRAP organised three virtual training sessions for the pharmaceutical industry on the 3rd, 10th and 19th of July, 2024. Approximately, 250 participants from the pharma industry were trained on the Pharmacovigilance Rules, 2022 relevant guidelines, and pharmacovigilance systems, including the collection and reporting of pharmacovigilance data. The outcome of these training sessions was to increase the ADR reporting by registration holders, contributing to the broader goal of enhancing ADR reporting rate in the country. The training schedule was as follows:

Region of the country	Training date
Registration holders of the Punjab	3rd of July, 2024
Registration holders of the Sindh.	10th of July, 2024
Registration holders of Islamabad, Khyber Pakhtunkhwa, Balochistan, Azad Jammu & Kashmir & Gilgit Baltistan.	19th of July, 2024

Minimum Standards for Establishment of Hospital Pharmacies in Pakistan

On 26th of December 2024, Division of Pharmacy Services, DRAP, alongside the WHO and Pakistan Society of Health-System Pharmacists (PSHP), organised a workshop in Islamabad to disseminate the Guidelines on Minimum Standards for Establishment of Hospital Pharmacies in Pakistan. Aligned with DRAP's mandate under the DRAP Act, 2012, the event aimed to enhance Pharmacy Services Nationwide by disseminating standards and building capacity among public and private sector hospital pharmacists.

The guidelines establish benchmarks for Hospital Pharmacy Services, enabling institutions to evaluate quality and ensure safe, effective, and cost-conscious medication use. The workshop focused on equipping pharmacists with practical skills to implement these standards, emphasising their role in optimising patient outcomes through management, medication safety, and antimicrobial stewardship.

The program opened with remarks from DRAP and WHO representatives, followed by an overview of the guideline development process led by Dr. Obaidullah, Director, DRAP, antimicrobial resistance surveillance by Dr. Aalia Zafar (WHO Country Office Pakistan) and DRAP's expectations for optimal medicine use by Mr. Abdul Mateen and Ms. Aqsa Hashmi (Deputy Directors, NPC, DRAP).

Subsequent sessions included presentations by Ms. Salwa Ahsan, Ms. Aasma Hamid and Ms. Sumaira Khan, experienced hospital pharmacy leaders from PSHP-affiliated institutions, elaborating different sections of the Guidelines. Each session was followed by a hands-on group exercise and team presentations. In these interactive exercises, participants applied the standards to case scenarios and discussed implementation challenges, reinforcing practical learning, concluding with a Q&A and post-test assessment.

Attendees spanned chief pharmacists, pharmacy managers, pharmacovigilance officers, and hospital pharmacists from hospitals and private facilities, reflecting nationwide engagement.

Speakers underscored that robust hospital pharmacies-aligned with national standards—are vital for patient safety and effective medication management. DRAP and WHO reiterated their commitment to elevating pharmacists' roles in multidisciplinary care, urging institutions to leverage their expertise fully. This initiative marks a critical step towards improving healthcare delivery in Pakistan by standardising Pharmacy Services and fostering interprofessional collaboration.

Statistics of National Pharmacovigilance System

Hospitals integrated into the VigiFlow database

The Punjab	1. Mayo Hospital Lahore 2. Holy Family Hospital, Rawalpindi 3. Rawalpindi Institute of Cardiology 4. DHQ, Sheikhupura 5. Ghurki Trust Teaching Hospital, Lahore 6. Services Hospital Lahore 7. Mian Meer Hospital Lahore 8. DHQ Hospital Nankana Sahib 9. Kot Khawaja Saeed Teaching Hospital, Lahore
Khyber Pakhtunkhwa	1. Hayatabad Medical Complex (HMC), Peshawar 2. Saidu Group of Teaching Hospital, Swat 3. District Headquarters Hospital, Kohat 4. Bacha Khan Medical Complex (BKMC), Swabi 5. Ayub Teaching Hospital, Abbottabad 6. Lady Reading Hospital (LRH), Peshawar 7. Alkhidmat Hospital, Peshawar 8. Khalifa Gul Nawaz Teaching Hospital (KGN), Bannu 9. Peshawar Institute of Medical Sciences, Peshawar 10. Rehman Medical Institute, Peshawar.
Azad Jammu and Kashmir	1. Abbas Institute of Medical Sciences (AIMS) Hospital, Muzaffarabad 2. Combined Military Hospital (CMH), Muzaffarabad 3. District Headquarters Hospital (DHQ), Jhelum Valley 4. District Headquarters Hospital (DHQ), Rawalakot 5. District Headquarters Hospital (DHQ), Sudhnoti 6. District Headquarters Hospital DHQ, Mirpur 7. District Headquarters Hospital (DHQ), Bhimber 8. District Headquarters Hospital (DHQ), Kotli 9. District Headquarters Hospital (DHQ), Haveli 10. District Headquarters Hospital (DHQ), Neelum 11. District Headquarters Hospital (DHQ), Bagh
Gilgit Baltistan	1. Agha Khan Health Services, Gilgit 2. Cardiac Hospital Jutial, Gilgit 3. RHQ Hospital, Chilas 4. PHQ Hospital, Gilgit 5. Kuwait Medical Complex, Skardu
Islamabad	1. Shifa International Hospital 2. Rawal General & Dental Hospital 3. Kulsum International Hospital 4. Ali Medical Centre

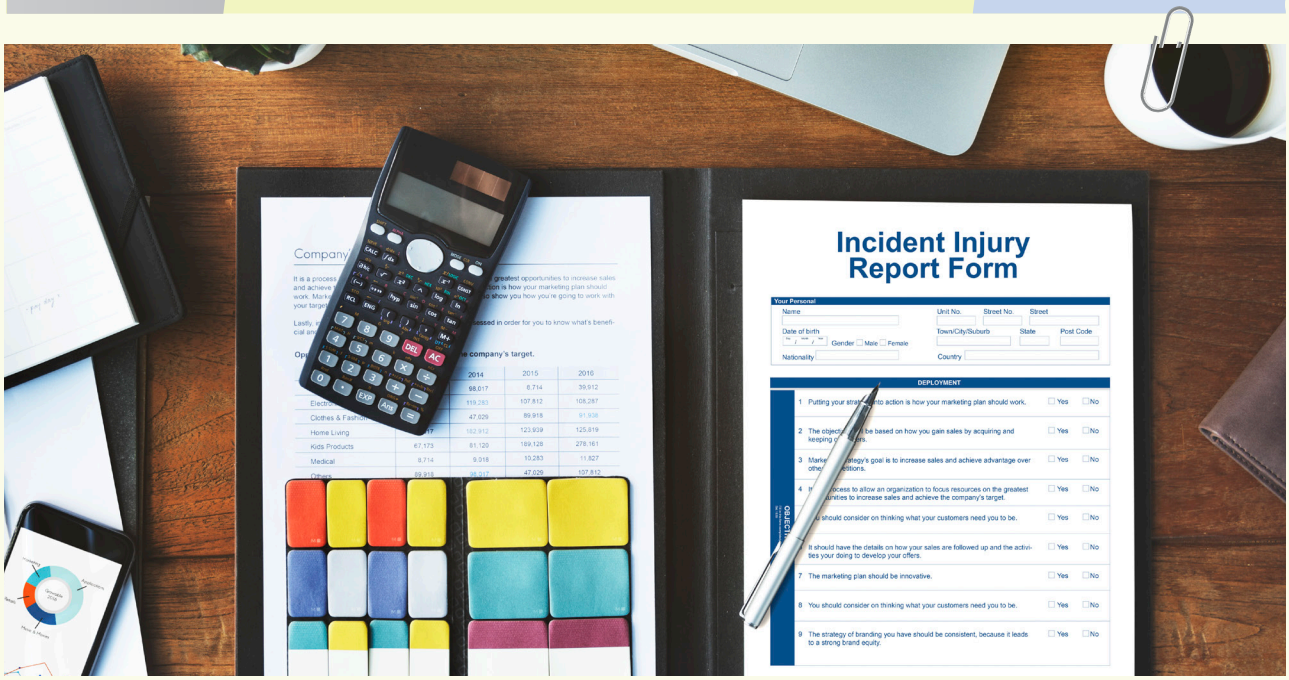
Top reporter from Sep-24 to April-25	
Name	No of reports
Aroosa Akber CPPO, Services Hospital Lahore	**43**

Top reporter from Sep-24 to April-25	
Name	No of reports
Mehwish Ilyas CPPO, Holy Family Hospital, Rawalpindi	**38**

53181
Total reports in VigiFlow, DRAP

Statistics of Reports as per 30th of April, 2025	
Stakeholders or Means of reporting	**No of reports.**
Federal Directorate of Immunization	32,186
Pharma Companies	19,025
The Punjab PV Centre	822
Islamabad PV Centre	696
E reporting and Mobile Application	448
Khyber PV Pakhtunkhwa Centre	4
Azad Jammu and Kashmir PV Centre	0
Gilgit Baltistan PV Centre	0

39,170
Reports Transferred to UMC



Safety Communication

Domestic Issues.

Serious Adverse Reactions with Ceftriaxone Injection due to Unintentional Mixing During Reconstitution.

The Provincial Pharmacovigilance Centre (PPC), Directorate of Drugs Control, Punjab, received reports of three children's deaths following injection Ceftriaxone administration at the District Headquarters Hospital Khanewal in June 2024. The children became unconscious and pulseless with fixed dilated pupils and absent cardiac activity immediately after injection. An investigation suggested the incident might have resulted from accidental mixing of High Alert Medications (HAMs) like Lidocaine, Potassium Chloride, or Amiodarone during reconstitution. The findings were presented at the 14th meeting of the Provincial Pharmacovigilance Committee (PVPC) on 29th of October, 2024. The PVPC proposed to DRAP that: a) Injection Potassium Chloride should be available in ready-to-use hydration form/pre-diluted solution instead of the currently available concentrated injection; b) Standardised branding with unique colour schemes and labelling should be adopted for critical injectables like Dextrose 25%, Sodium Bicarbonate, and Potassium Chloride.

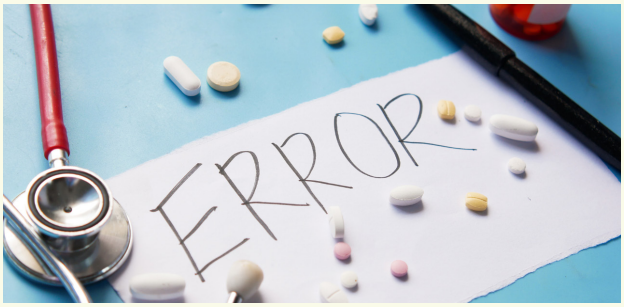
The case was further reviewed in the 5th meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC), DRAP, on 2nd of January, 2025. The PRAEC endorsed PVPC's recommendations and, under Rule 10(1)(e) of the Pharmacovigilance Rules, 2022, recommended that the Registration Board may take necessary measures to ensure the availability of ready-to-use Potassium Chloride solutions. It was also instructed that the National Pharmacovigilance Centre should develop a proposal for distinct branding and labelling of concentrated electrolytes.

Healthcare professionals should inform patients about the risk of anaphylactic reactions with Ceftriaxone, take a detailed drug allergy history, and administer a test dose before use. In Hospitals, storage of concentrated electrolytes must be closely monitored. Potassium Chloride should be removed from ward stocks/patient bedside and issued by the pharmacy on a patient-specific basis with clear labelling to minimise medication errors.

International Safety Issues

Risk of Medication Errors Resulting due to Inadvertent Intrathecal Tranexamic Acid Injection

The WHO, in its medical product alert on the 16th of March, 2022, warned of the risk of administration errors with tranexamic acid (TXA) injections, highlighting reports where TXA was mistakenly given intrathecally instead of spinal anaesthesia, leading to severe neurological consequences and high mortality. The WHO also noted that TXA is often stored near similar-looking local anaesthetics, increasing the risk of such errors. In May 2024, SAHPRA of South Africa updated the labels of tranexamic acid injection with "HIGH ALERT" and "For IV Use Only" to prevent errors. Healthcare professionals were advised to store ampoules separately, verify labels before use, label syringes clearly, and use barcode scanning or double-checking when preparing medication.

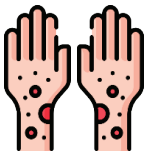


Previously, the PRAEC in its 4th meeting had recommended to the National Pharmacovigilance Centre (NPC) to issue a safety alert/ advisory related to the risk of medication errors due to inadvertent intrathecal tranexamic acid injection. In its 5th meeting on 2nd January 2025, the PRAEC further advised NPC to coordinate with Provincial Health Departments and hospitals to improve storage practices, apply distinct labelling, and implement double-checking procedures to minimise the risk of such medication errors.

Tranexamic acid (TXA) is used to prevent and treat haemorrhages from fibrinolysis, including in gynaecological surgery and postpartum haemorrhage.

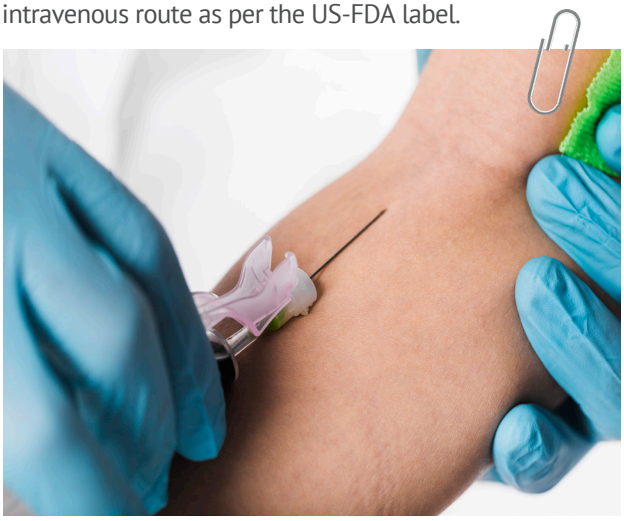
Healthcare professionals working in operation theatres should verify TXA labelling before administration to avoid accidental intrathecal injection, which can cause severe neurotoxicity. Reviewing and adjusting drug handling practices, including storing TXA away from the anaesthetic drugs trolley, is recommended to reduce this risk. Hospitals are advised to enhance the storage practices for tranexamic acid injection, along with distinct labelling and double-checking product labels when stocking medication cabinets and preparing medication for injection and before administration.

Risk of Severe Chemical Irritation and Damage to Tissues with Promethazine Hydrochloride Injection



In December 2023, the US-FDA issued a warning to healthcare professionals about updated labelling for Promethazine hydrochloride injection to reduce the risk of severe chemical irritation and tissue damage from intravenous administration. Key points include: If intramuscular injection is not possible, Promethazine hydrochloride can be administered intravenously only after dilution, using a large vein or central venous catheter, not veins in the hand or wrist; It should not be mixed with other drugs or diluted with anything other than 0.9% sodium chloride; It is contraindicated for IV use at concentrations greater than 1 mg/mL; and when infused, the injection should be administered over 20–40 minutes.

In the 5th PRAEC meeting held on 2nd of January 2025, it was decided that registration holders of Promethazine hydrochloride injection should include information related to the risk of severe chemical irritation and damage to tissues when administered through the intravenous route as per the US-FDA label.



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

Healthcare professionals should administer Promethazine hydrochloride via deep intramuscular injection rather than intravenously. If intravenous administration is necessary, healthcare professionals should review and follow the updated information in the labelling, i.e. to dilute Promethazine hydrochloride injection and administer it by intravenous infusion to reduce the risk of severe tissue injury.

Risk of Pathological Gambling with Aripiprazole

In December 2023, the MHRA-UK alerted healthcare professionals to the known risk of addictive gambling with Aripiprazole following an increase in reports in 2023. Between 30th June, 2009 to 28th August, 2023, 69 Yellow Card reports cited Aripiprazole for gambling-related side effects, primarily in individuals aged 20 to 40 years, many without a prior gambling history. In most cases, stopping Aripiprazole led to a reduction or cessation of gambling urges. It was informed that since early 2023, an uptick in reports of gambling, gambling disorder, and obsessive-compulsive disorder has been noted. The Neurology, Pain, and Psychiatry Expert Advisory Group (NPPEAG) reviewed the issue and noted that the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) already warn of impulse control disorders. The NPPEAG recommended that the MHRA-UK remind healthcare professionals and patients about these risks.

In its 5th meeting held on 2nd of January 2025, the PRAEC committee of the DRAP recommended that the National Pharmacovigilance Centre should issue a safety alert to raise awareness among healthcare professionals and patients about the known risk of addictive gambling associated with Aripiprazole

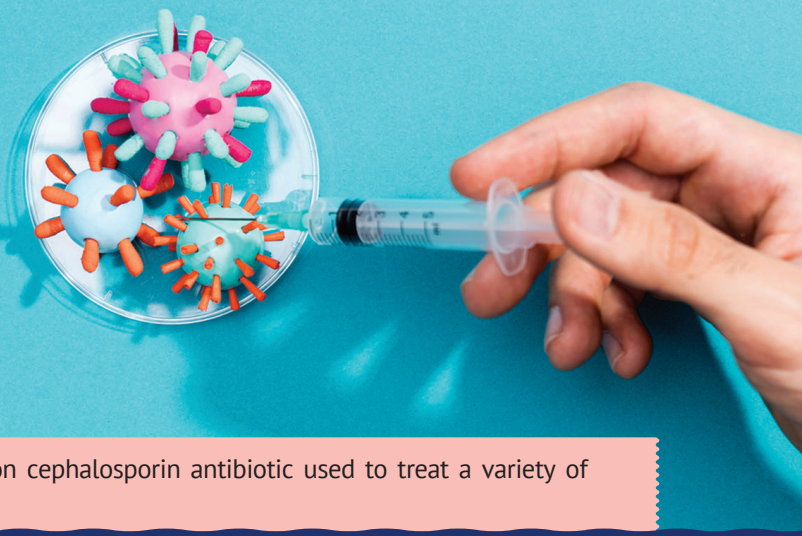
Aripiprazole is an antipsychotic medication with three approved indications: treatment of schizophrenia in adults and adolescents over 15, short-term treatment of moderate to severe manic episodes in Bipolar-I disorder in adults and adolescents over 13, and prevention of new manic episodes in adults who responded to Aripiprazole for prior manic episodes.

Reports of gambling disorder and pathological gambling associated with Aripiprazole have increased in the UK and involved both patients with and without a prior history of gambling issues, and most cases resolved upon dose reduction or discontinuation. **Healthcare professionals** should advise patients and caregivers to monitor for new or increased urges to gamble or other impulse control symptoms, such as excessive eating, spending, or an abnormally high sex drive. If these occur, consider dose reduction or discontinuation, but patients should consult their doctor before stopping Aripiprazole. **Patients** should inform their doctor of any history of excessive gambling or impulse control disorders before starting treatment, and notify them if unusual behaviours are noticed.

Risk of Severe Cutaneous Adverse Reactions with Cefotaxime.

In its January 2024 meeting, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recommended updating Cefotaxime product information to strengthen warnings on severe cutaneous adverse reactions (SCARs), including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms). DRESS should be listed as an adverse drug reaction (ADR) with a frequency of "Not known." The warnings should highlight that SCARs, such as acute generalised exanthematous pustulosis (AGEP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS can occur, which can be life-threatening or fatal. Patients should be informed about the signs of skin reactions, and Cefotaxime should be discontinued immediately if symptoms appear. Re-treatment must not occur if SCARs develop. In children, physicians should carefully differentiate between rash due to infection and drug reactions.

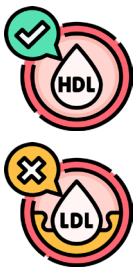
In Pakistan, the case was discussed in the 5th meeting of PRAEC held on 2nd of January 2025, and it was decided that registration holders should update Cefotaxime prescribing information to include SCARs warnings and list DRESS as an ADR with unknown frequency.



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

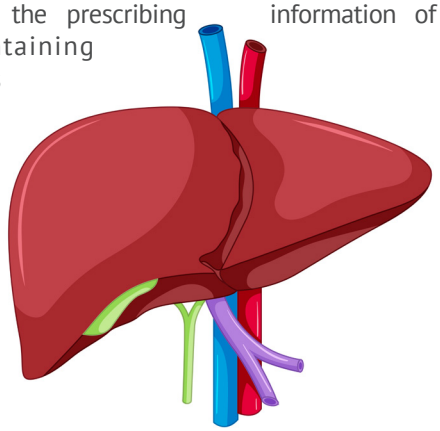
Healthcare professionals are informed that SCARs, including AGEP, SJS, TEN, and DRESS, have been reported with Cefotaxime, which can be life-threatening. Patients should be informed of skin reaction symptoms at the time of prescription. Cefotaxime must be discontinued immediately if symptoms appear and must not be restarted if SCARs occur. In children, rashes may be mistaken for infections; clinicians should consider SCARs if rash and fever develop during treatment. **Patients** are advised to stop Cefotaxime and seek immediate medical attention if signs of serious skin reactions occur and to inform their doctor if they have a history of severe skin reactions to Cefotaxime or other cephalosporins.

Risk of Drug-Induced Liver Injury (DILI) and Severe Cutaneous Adverse Reactions (SCARs) with Ezetimibe.



In March 2024, Health Canada updated the product information for Ezetimibe (Ezetrol®) to include warnings about serious adverse reactions, including drug-induced liver injury (DILI) and severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilic and systemic symptoms (DRESS). A review of international safety data identified 42 post-marketing cases of DILI linked to Ezetimibe, supporting a causal association even with monotherapy. Consequently, the current recommendation to consider performing liver function tests at the initiation of, or during treatment with Ezetimibe in combination with a statin or fenofibrate has been expanded to also include Ezetimibe monotherapy. Furthermore, rare cases of SCARs were also identified with evidence suggesting a possible causal link to Ezetimibe.

The case was discussed in the 5th meeting of the PRAEC, which decided that registration holders should include warnings about serious adverse reactions, including DILI and SCARs, to the prescribing information of Ezetimibe-containing medicines (monotherapy or in combination) in the adverse drug reaction and warning and precaution sections.



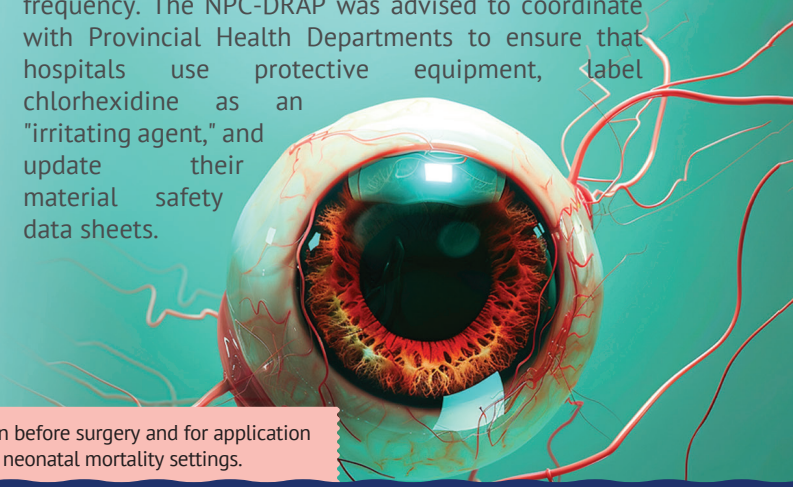
Ezetimibe, a cholesterol absorption inhibitor, is indicated as an adjunct to diet and lifestyle changes for the treatment of primary hypercholesterolemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia (phytosterolemia) when non-pharmacological measures are inadequate.

Healthcare professionals are advised to perform liver function tests at the initiation of treatment with Ezetimibe (whether used alone or with a statin or fenofibrate) and as needed thereafter. Patients should be instructed to immediately report symptoms of liver injury or severe skin reactions (SCARs) and discontinue Ezetimibe if these occur. Patients are informed that serious risks include drug-induced liver injury and severe skin reactions, including SJS and TEN have been reported with Ezetimibe. **Patients** should immediately consult their Doctors if symptoms like severe abdominal pain, dark urine, yellowing of the skin or eyes and/or skin reactions such as blistering, swelling or fever occur.

Risk of Persistent Corneal Injury and Significant Visual Impairment with Chlorhexidine (cutaneous use).

The PRAC-EMA, in April 2024, recommended updating product information for chlorhexidine topical use products to highlight the risk of persistent corneal injury and significant visual impairment. Post-marketing reports of severe corneal erosion and permanent vision loss following accidental ocular exposure have, in some cases, led to corneal transplantation. MAHs should update product warnings, emphasising that chlorhexidine must not contact the eyes, that serious injuries can occur despite protective measures, and that extreme caution is needed during application, particularly in anaesthetised patients. In case of eye exposure, the affected area must be rinsed thoroughly with water, and an ophthalmologist consulted. It was also decided that the "undesirable effects" section of the label should include corneal erosion, epithelial defects, and permanent visual impairment, with frequency as "not known." In August 2020, the WHO issued an alert regarding cases of severe eye injuries caused by the incorrect route of administration of chlorhexidine gluconate (CHX) to the eyes of newborns instead of the umbilical cord. Clean, dry cord care remains the standard for newborns in healthcare settings and at home in low neonatal mortality settings, with CHX recommended only where harmful traditional practices exist. Since 2015, over 40 cases of CHX-related eye injury have been reported globally, involving both liquid and gel formulations, where CHX was mistaken for eye products. Healthcare providers, caregivers, and distributors are urged to exercise extreme caution to ensure correct CHX use. WHO recommends assessing CHX packaging to prevent confusion, updating product labels, developing clear, culturally appropriate educational materials, and training healthcare professionals on proper use.

In its 5th meeting, the PRAEC decided that registration holders should update the warning and precaution sections of Chlorhexidine products for skin disinfection and list corneal erosion, epithelial defect/corneal injury, and significant permanent visual impairment as adverse events with an unknown frequency. The NPC-DRAP was advised to coordinate with Provincial Health Departments to ensure that hospitals use protective equipment, label chlorhexidine as an "irritating agent," and update their material safety data sheets.



Chlorhexidine is an antiseptic and disinfectant used for skin disinfection before surgery and for application to the umbilical cord stump of newborns who are born at home in high neonatal mortality settings.

Healthcare professionals are advised that Chlorhexidine must not come into contact with the eyes, as accidental ocular exposure has led to serious and persistent corneal injuries, sometimes requiring corneal transplantation. Such incidents have occurred even when eye protection was used, due to migration of the solution beyond the intended surgical site. Extreme care must be taken when applying, particularly in anaesthetised patients who cannot report exposure. If Chlorhexidine contacts the eyes, immediately and thoroughly rinse with water and seek an ophthalmologist's advice. **Patients** are also advised to speak with their doctor, pharmacist, or nurse before using Chlorhexidine and to seek prompt medical attention if irritation, redness, pain, or visual disturbances occur.

Potential Risk of Tumour Lysis Syndrome with Sorafenib.

Health Canada, through its June 2024 Infowatch Newsletter, highlighted a potential risk of Tumour Lysis Syndrome (TLS) with Nexavar (Sorafenib), triggered by a labelling update from the EMA and international case reports. A review of nine international cases, including eight from the literature, suggested a possible link between sorafenib and TLS. Onset ranged from 3 to 34 days after treatment, with five deaths possibly related to TLS, though other causes, like cancer progression, could not be ruled out. It was informed that Health Canada is working with the manufacturer to update Sorafenib's product information to include TLS as a risk.

Previously, in February 2022, the EMA's PRAC committee reviewed available data and recommended adding TLS to the warning and precaution sections of Sorafenib's label. PRAC advised close monitoring for patients with risk factors, such as high tumour burden or renal insufficiency, and recommended prophylactic hydration. TLS should also be listed in the ADR section with an "unknown" frequency. The TLS occurs when cancer cells break down rapidly during treatment, releasing substances that can overwhelm the kidneys and other organs, potentially causing severe damage.

In its 5th meeting, the PRAEC decided that registration holders should update Sorafenib's product information to include the risk of Tumour Lysis Syndrome (TLS) in the warning and precaution section and also list TLS in the ADR section with an "unknown" frequency.

Sorafenib is used for the treatment of hepatocellular carcinoma (that cannot be treated by surgery), late-stage renal cell carcinoma and late-stage thyroid carcinoma.

Healthcare professionals informed about fatal cases of TLS reported in patients treated with Sorafenib. Risk factors include high tumour burden, renal insufficiency, dehydration, hypotension, and acidic urine. Close monitoring, prompt treatment, and prophylactic hydration are recommended. **Patients** should seek immediate medical attention if they experience nausea, shortness of breath, irregular heartbeat, muscle cramps, seizures, cloudy urine, or fatigue, as these could indicate TLS, which may lead to kidney damage and acute renal failure.

Suspension of Marketing Authorisations of 17 Hydroxyprogesterone Caproate (17-OHPC) due to its Ineffectiveness in Authorised Uses.

In May 2024, the PRAC-EMA recommended the suspension of marketing authorisations for medicines containing 17-hydroxyprogesterone caproate (17-OHPC). This decision followed a study suggesting a possible increase in cancer risk in those exposed to 17-OHPC in the womb, though the study's limitations made a definitive conclusion impossible. The PRAC also found that 17-OHPC is no more effective than a placebo in preventing premature births, with limited evidence supporting its effectiveness for other uses. Given the possible cancer risk and the lack of proven benefits, PRAC concluded that the risks outweighed the benefits, recommending the suspension of its marketing authorisation.

Similarly, in April 2023, the US-FDA withdrew approval of Makena (Hydroxyprogesterone Caproate), a drug approved under the accelerated approval pathway in 2011, based on an intermediate clinical endpoint, with a requirement to conduct post-marketing confirmatory studies. However, the confirmatory study did not prove clinical benefit, leading the FDA to propose withdrawal in 2020. After a hearing in 2022 and further review, the FDA determined that Makena and its generics were ineffective, and the benefits did not outweigh the risks, resulting in the withdrawal of approval.

In its 5th meeting held on 2nd January, 2025, the PRAEC recommended suspension of 17-hydroxyprogesterone caproate (17-OHPC) in Pakistan due to potential cancer risks in those exposed in the womb and lack of effectiveness in the approved indications. The PRAEC recommended to the Registration Board to suspend the registration of 17-OHPC containing medicine in Pakistan as per procedure. Accordinlgy, the Registration Board in its 346th meeting, held on 22nd April, 2025, suspended the registration of 17-OHPC medicines in Pakistan, after giving a personal hearing to firms.

17-hydroxyprogesterone caproate (OHPC) is a synthetic progesterone used to prevent pregnancy loss and premature birth. It is also authorised to treat various gynaecological and fertility disorders related to progesterone deficiency.

Healthcare professionals are informed that 17-OHPC-containing medicines are suspended in Pakistan due to potential cancer risks and lack of effectiveness in the approved indications. Healthcare professionals should stop prescribing 17-OHPC and consider alternatives. **Patients** should stop using 17-OHPC and consult their doctors for other treatment options available. The patient should not confuse 17-OHPC with progesterone, which works differently.

Risk of Meningioma with Medroxyprogesterone Acetate.

In September 2024, the European Medicines Agency's PRAC recommended measures to minimise the risk of meningioma (a brain tumour) with high-dose Medroxyprogesterone Acetate (MPA). Data showed an increased risk with long-term use of high doses, although the absolute risk is small. The PRAC advised against using MPA in patients with a history of current or past meningioma, unless required for oncological treatment, and recommended monitoring for symptoms such as vision changes, hearing loss, headaches, memory loss, seizures and weakness in arms and legs. Likewise, in October 2024, Health Canada updated the Canadian product monographs for MPA to include the risk of meningioma. It also recommended discontinuing MPA if a meningioma is diagnosed and exercising caution in patients with a history of meningioma. Meningiomas are typically benign tumours that grow slowly but can cause serious issues depending on their size and location.

Accordingly, the PRAEC, decided that registration holders should update product information for medicines containing MPA by including the risk of "Meningioma" in the warning and precaution section.

Medroxyprogesterone acetate (MPA) is a medicine which is used for gynaecological (including contraception and endometriosis) and oncological indications.

Healthcare professionals are informed that prolonged use of medroxyprogesterone acetate has been linked to cases of meningioma (single and multiple). Patients should be monitored for signs of meningioma. If diagnosed with meningioma, treatment should be discontinued, except for oncological indications, where the need for continuation should be carefully assessed. **Patients** are advised not to use MPA if they have a history of meningioma, unless for cancer treatment. If symptoms like vision changes, hearing loss, headaches, memory loss, seizures or weakness in your arms or legs occur, you must tell your doctor straightaway.

ڈرگ ریگولیٹری اتھارٹی آف پاکستان
وزارت نیشنل ہیلتھ سروسز، ریگولیشنز اور کوآرڈینیشن

فارماکوویجیلنس
نیوزلیٹر

شمارہ: ۱ | مئی: ۲۰۲۵ | والیم: ۳

ڈرگ ریگولیٹری اتھارٹی آف پاکستان نے #MedSafetyWeek 2024 سوشل میڈیا مہم میں حصہ لیا۔

ڈرگ ریگولیٹری اتھارٹی آف پاکستان(ڈریپ) نے #MedSafetyWeek 2024 کے موقع پر ادویات کی حفاظت اور دوائیوں کے مضر اثرات کی رپورٹنگ کی اہمیت کے بارے میں آگاہی پھیلانے کے لیے ایک متحرک سوشل میڈیا مہم کا اہتمام کیا۔ 4 تا 10 نومبر 2024 تک منائے جانے والے اس عالمی اقدام میں ڈریپ نے ہیلتھ کیئر پیشہ ور افراد، مریضوں، اور بین الاقوامی ریگولیٹرز کے ساتھ مل کر "آپ کی رپورٹ زندگیاں بچاتی ہے: محفوظ ادویات کے لیے آواز اٹھائیں" کے موضوع کے تحت ادویات کے محفوظ استعمال کو فروغ دیا۔

ڈریپ نے سوشل میڈیا مہم میں کیسے حصہ لیا؟

ڈیجیٹل پلیٹ فارمز کی طاقت کو بروئے کار لاتے ہوئے، ڈریپ نے فیس بک، لنکڈ ان، اور، ٹویٹر / ایکس پر عوامی آگاہی کے لیے دلچسپ مواد شیئر کیا۔ نمایاں اقدامات میں شامل تھے:- * اینیمیٹڈ انفوگرافکس * : رنگین اینیمیشنز کے ذریعے ادویات کے مضر اثرات کی رپورٹنگ کے مراحل، ادویات کو محفوظ طریقے سے رکھنے، اور لیبلز پڑھنے کی اہمیت کو واضح کیا گیا۔ مزید برآں، علاقائی زبانوں میں مضر / ضمنی اثرات کی رپورٹنگ سے متعلق آگاہی ویڈیوز بھی سوشل میڈیا کے ذریعے شیئر کی گئیں۔

رپورٹنگ کیوں ضروری ہے؟

غیر رپورٹ شدہ مضر / ضمنی اثرات عوامی صحت کو خطرے میں ڈال سکتے ہیں۔ ڈریپ نے اپنے پلیٹ فارمز کے ذریعے ادویات کے مضر / ضمنی اثرات کی رپورٹنگ کو (ویب سائٹ اور موبائل ایپ کے ذریعے) فروغ دیا، جہاں مریض اور پیشہ ور افراد منٹوں میں رپورٹ جمع کرا سکتے ہیں۔

مہم میں نمایاں کیے گئے اقدامات:

۱۔ پہچان: دوائی لینے کے بعد غیر معمولی علامات پر نظر رکھیں۔
۲۔ رپورٹ: VigiMobile کے ذریعے منفی اثرات کی تفصیلات ہمارے پاس جمع کروائیں یا اپنے ڈاکٹر کو مطلع کریں۔
۳۔ ردعمل: ڈریپ تحقیقات کر کے حفاظتی ہدایات اپڈیٹ کرتا ہے۔

مہم میں کیسے شامل ہوں؟

اگرچہ #MedSafetyWeek2024 کا اختتام ہو چکا ہے، لیکن ڈریپ عوام سے مستقل احتیاط کی اپیل کرتا ہے:

فیصلہ کریں: ڈریپ کے سوشل میڈیا پیجز کو فالو کریں۔

ڈاؤن لوڈ کریں: VigiMobile۔

- آگاہ کریں: ڈریپ کے مفت وسائل استعمال کر کے اپنی کمیونٹی کو تعلیم دیں۔

ادویات کے مضر / ضمنی اثرات کی اطلاع دے کر، آپ ریگولیٹرز کو ادویات کے خطرات پر عمل کرنے کے لیے بااختیار بناتے ہیں- تاکہ دوائیں بیماری کے خلاف ایک ڈھال بنیں، نہ کہ خود ایک خطرہ بنیں

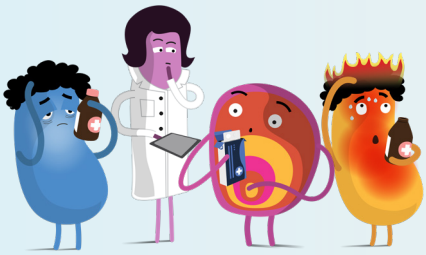
ہم امید کرتے ہیں کہ آپ اور آپ کی تنظیم آنے والے سالوں میں ادویات کی حفاظت سے متعلق ڈریپ کی سوشل میڈیا مہم کا حصہ بنیں گے۔

محفوظ رہیں۔ باخبر رہیں۔ آواز اٹھائیں۔

"مضر / ضمنی اثرات کی ہر رپورٹ عوام کی صحت کی حفاظت کے لیے اہم ہے، آیئے سب مل کر ادویات کے خطرات کی جلد شناخت کر کے جانیں بچائیں۔"

ڈاکٹر عبید اللہ، سی ای او، ڈریپ

VigiMobile
ایپلیکیشن ڈاؤن لوڈ کرنے کے لیے کوڈ اسکین کریں۔



Uppsala Monitoring Centre #MedSafetyWeek