DRUG REGULATORY AUTHORITY OF PAKISTAN
NATIONAL PHARMACOVIGILANCE CENTRE

PHARMACOVIGILANCE NEWSLETTER

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Global Recognition: WHO Highlights DRAP's Pharmacovigilance Excellence in its Pharmaceuticals Newsletter 04/2023

The World Health Organization (WHO) in its Pharmaceuticals Newsletter 04/2023 (Case No 8, Page 6) published the ADR signal of Hypersensitivity reaction with Pegasperginase (an anti-cancer biological drug) identified by the National PV Centre, DRAP. The publication in the Newsletter is a sign of the professional and dedicated work of DRAP's Pharmacovigilance team and international recognition and acknowledgement of work by the WHO. The National Pharmacovigilance Centre is committed to ensuring the safety of therapeutic goods in Pakistan through continuous safety monitoring, detecting the domestic signals and minimization of the risks associated with the use of therapeutic goods. NPC would like to encourage healthcare professionals and patients to report any adverse event they experience through the available channels and contribute their part in the safety monitoring.

World Health Organization

WHO Pharmaceuticals NEWSLETTER

2023 No. 4

Pegaspargase

Risk of hypersensitivity reactions

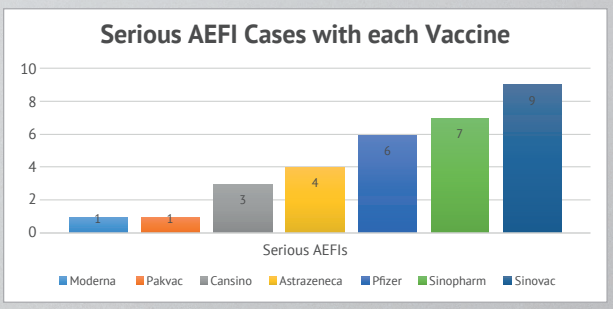
Pakistan. The National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP) has announced that the product information for pegaspargase should be updated to include the risk of hypersensitivity reaction.

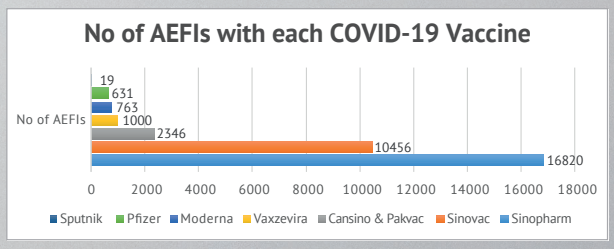
Pegaspargase is indicated for the treatment of acute lymphoid leukaemia in paediatric and adult patients who have hypersensitivity to the native forms of L-asparaginase.

The NPC-DRAP reviewed six case reports of hypersensitivity reactions with pegaspargase injection used in children with acute lymphoid leukaemia occurring within one day of the administration. All cases were evaluated as having a possible relationship between the medicine and events. The Pharmacovigilance Risk Assessment Expert Committee decided to update the product information to include the risk of hypersensitivity reaction together with the advice on monitoring and treatment modification as per the grade of hypersensitivity reaction.

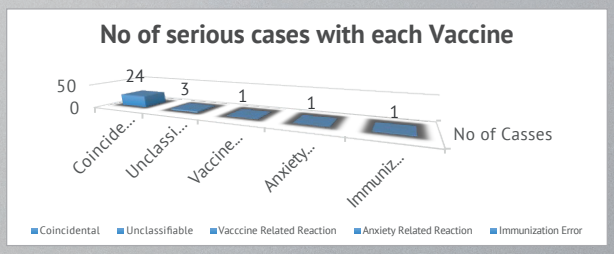
COVID-19 Vaccines in Pakistan: Safety Report

Pakistan recorded 1,580,631 COVID-19 cases with 30,656 fatalities from 3 January, 2020 till 13th November, 2023 (1). Global efforts initially explored diverse treatment regimens, but due to promising vaccine trial results, countries granted Emergency Use Authorization (EUA) to COVID-19 vaccines for a return to normalcy and risk reduction. The Drug Regulatory Authority of Pakistan (DRAP) played a key role in responding to the pandemic by approving trials and ensuring timely access to treatments. DRAP granted EUA to vaccines like Sinopharm, CanSino Biologics' Convidecia, Sinovac Lifesciences' CoronaVac, Serum Institute of India's Covishield, Pfizer-BioNTech's Comirnaty, and Sputnik's Gam-COVID-Vaccine (2). The government of Pakistan also received donations of AstraZeneca's Vaxzevria, Pfizer's Comirnaty, and Moderna's Spikevax vaccines from various health partners. The vaccination drive, starting in February 2021 with Sinopharm was managed by the Federal Directorate of Immunization (FDI) through dedicated adult vaccination counters nationwide.





The EUA for COVID-19 vaccines was granted due to their favourable risk-benefit profile compared to the potential risk associated with contracting COVID-19. To ensure public safety and trust, monitoring adverse events following immunization (AEFI) data became essential. In Pakistan, AEFIs were collected through various channels by FDI, including the National Immunization Management System, the Sehat Tahaffuz helpline 1166, EPI-MIS, COVIMS and others. The collected data is then shared with the National Pharmacovigilance Centre (NPC) by the FDI for international dissemination (3).



With a population of 228.5 million, 90% of the eligible 143.1 million individuals in Pakistan are fully vaccinated. A total of 307,169,997 vaccine doses, including boosters, have been administered. The FDI received 129,205 AEFIs, of which 31 were serious and 129,174 minor. Among the reported AEFIs, vaccination site reactions, slight fever, and headache predominated. Skin rash/allergy, nausea, vomiting, and diarrhoea were reported, albeit not as frequently. Other reactions such as local pain, muscle pain, and serious cases were infrequent, aligning with typical immune responses that resolve within days (4).

Out of 32,127 AEFI reports received at NPC, 31 cases have been classified as serious AEFIs by an independent National AEFI review committee working under the Ministry of National Health Services Regulation and Coordination. The serious cases inter-alia include acute myocardial infarction, coronary artery atherosclerosis, haemorrhagic stroke, guillain barre syndrome, Bell's palsy, arthralgia, ovarian cysts and heavy menstrual bleeding etc. The majority of these serious AEFIs i.e. 24 cases were classified as coincidental, 3 as un-classifiable, 1 as immunization error, 1 anxiety-related event and 1 vaccine-related reaction. 16 out of 31 serious cases have been reported with the inactivated vaccines of Sinopharm and Sinovac, 7 cases have been reported with the mRNA-based vaccine of Comirinty (Pfizer) and Spikewax (Moderna) and the remaining 8 cases with viral vector-based vaccines such as Convidecia & PakVac (CanSino Biologics) Sputnik's Gam-COVID-Vaccine and Vaxzevria (AstraZeneca) (5).

Vaccines, including those for COVID-19 in Pakistan, may have side effects, with common ones being vaccination site reactions, headache, fever, slight fever, diarrhoea, skin rash, nausea, and vomiting. These reactions are generally not linked to severe illness but reflect a normal immune response. The DRAP and FDI continually monitor vaccine AEFIs, emphasizing that their benefits outweigh known side effects. The NPC, DRAP, advises vaccinating staff to report AEFIs via the NIMS database to FDI and also encourages vaccinated individuals to report any AEFI to NPC through the E-reporting system or Med Safety Mobile application on Android and iOS platforms.

References:

1. WHO dashboard for COVID-19 disease: Pakistan.
2. Minutes of Registration Board of the DRAP.
3. Revised National Guidelines for AEFI by Federal Directorate of Immunization.
4. National update data of COVID-19 Vaccination & AEFI Surveillance by Federal Directorate of Immunization.
5. VigiFlow database of National Pharmacovigilance Centre.

DRAP Celebrated #MedSafetyWeek in Collaboration with the Uppsala Monitoring Centre.

The Drug Regulatory Authority of Pakistan (DRAP) participated in the #MedSafetyWeek 2023 (6th to 12th November 2023) to raise awareness and encourage everyone to report suspected side effects of medicines.

#MedSafetyWeek is an International social media campaign led by the Uppsala Monitoring Centre (UMC), the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring (PIDM). The campaign is run in collaboration with National Pharmacovigilance Centres (NPC), Medicines Regulatory Bodies and several non-governmental organisations.

The goal of #MedSafetyWeek this year was to get patients and healthcare professionals to report suspected side effects of medicines. The campaign material focused on the theme 'Who can report?' by focusing on the key role of every patient, doctor, nurse, and pharmacist who reports a side effect and contributes to using medicines safely.

The campaign was carried out through the official social media channels of DRAP (Twitter, Facebook and LinkedIn) to convey the message that patients/caregivers and all healthcare professionals can report suspected side effects to the National Pharmacovigilance Centre, DRAP.

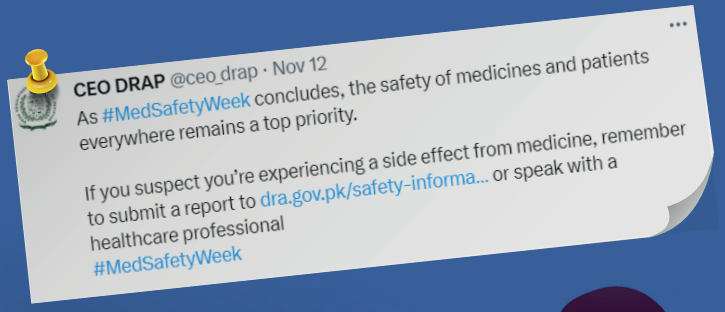
DRAP has multiple reporting tools in place which are freely accessible for use and reporting directly to the NPC. You can submit a report in many ways:

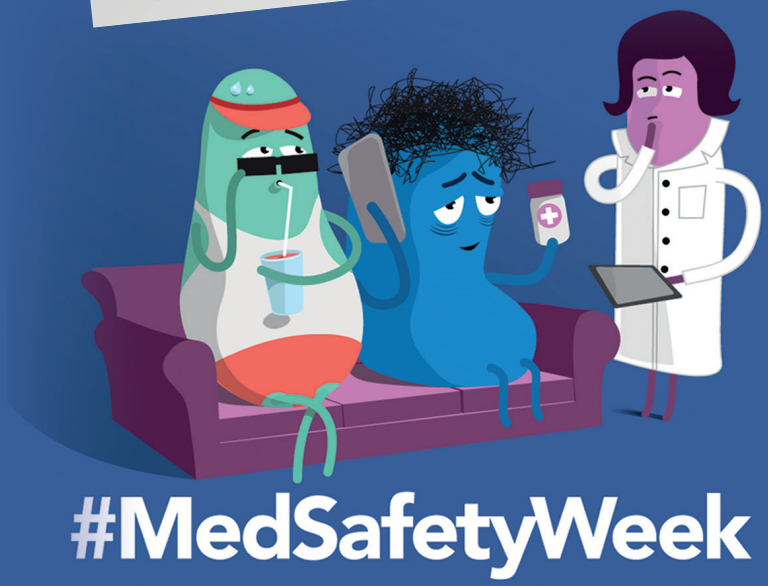
- **Med Safety Mobile App (Android/iOS)**
- **Med Vigilance E-Reporting System**
- **Yellow reporting form**
- **Email: npc@dra.gov.pk**
- **Landline: 051-9255981**

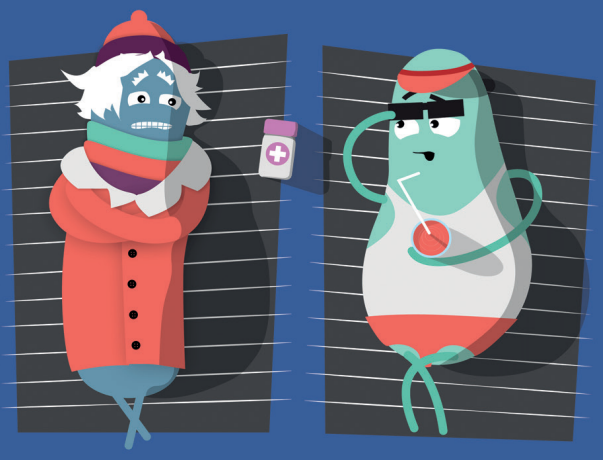
DRAP has the responsibility to operate systems to detect and analyse the side effects of medicines. The purpose of safety monitoring is to gain more information about known side effects and find out about new ones. Constantly collecting and monitoring information from the reports received helps identify risks associated with medicines and take action to minimise harm.

All reports made to NPC-DRAP are thoroughly assessed and examined to determine the right steps to be taken to protect the population from harm. It is pertinent to mention that since 2018, the NPC DRAP has received 48707 reports in which patients & healthcare professionals (295 reports), provincial pharmacovigilance centres of Punjab and Islamabad (834 reports), federal directorate of immunization (32127 reports) and registration holders (15451) have played a key role.

Play your part in medicines safety. Whether you're a patient, doctor, nurse, or pharmacist, you can help make medicines safer by reporting side effects to the National Pharmacovigilance Centre and DRAP.





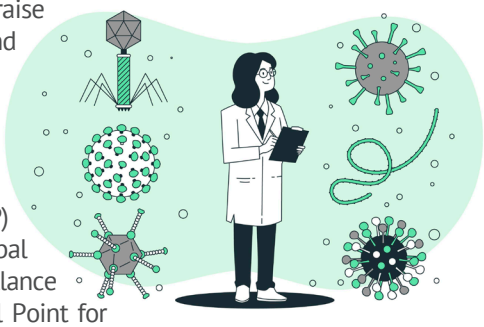


Antimicrobial Resistance (AMR): A Global Challenge

Microbes play a crucial role in our bodies, with unique microbial communities colonizing us from birth and aiding in digestion and disease protection. However, certain microbes can cause infectious diseases ranging from mild to severe. These include bacteria, viruses, fungi and protozoa. To combat such infections, antimicrobial agents like antibiotics, antivirals, antifungals, antiprotozoals and vaccines have been developed, significantly improving human health. Unfortunately, the widespread use and misuse of these agents have led to the emergence of antimicrobial resistance (AMR).

Microorganisms' success is attributed to their adaptability through genetic mutation and the transfer of genetic material. When faced with threats, microbes undergo rapid genetic mutation, equipping them with protective mechanisms. This adaptability has given rise to AMR, a global threat rendering various infections difficult to treat, potentially leading to prolonged hospital stays and even death.

The seriousness of AMR prompted global initiatives, such as the Global Action Plan on AMR and World Antimicrobials Awareness Week (WAAW), observed from 18th to 24th November every year. Organizations worldwide focus on eradicating AMR through the One Health concept, involving human, animal, food, and environmental factors. The World Health Organization plays a key role in coordinating efforts to raise awareness and implement strategies.

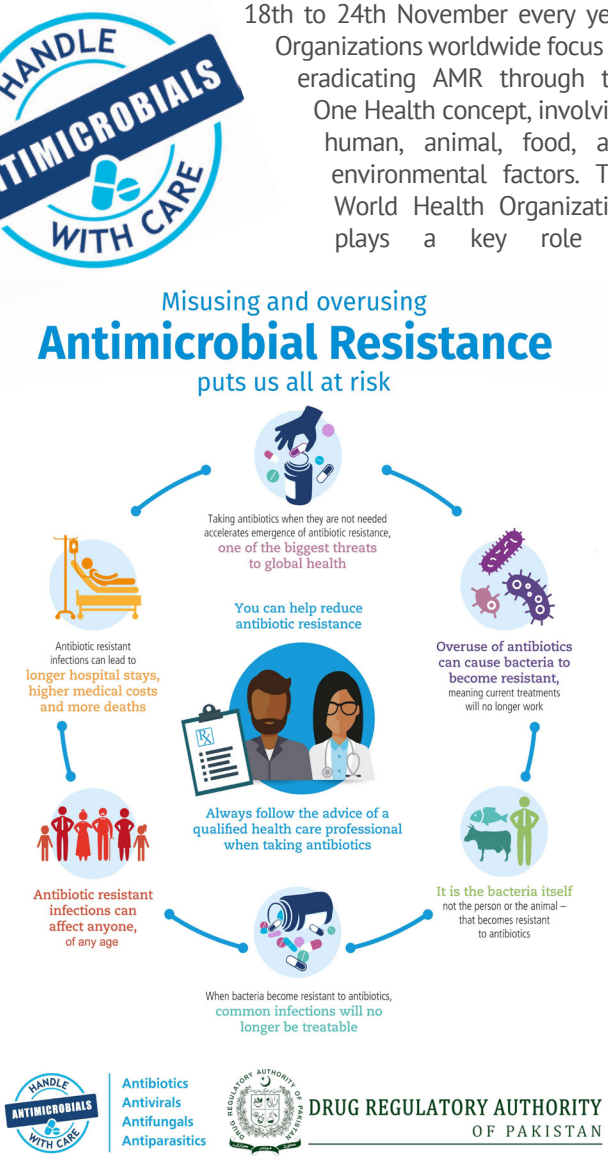


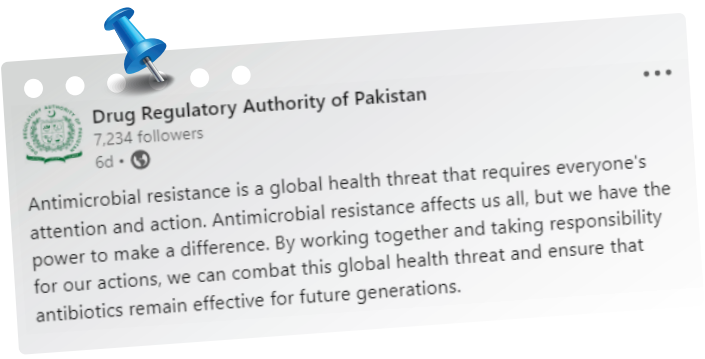
In the context of Pakistan, the Drug Regulatory Authority of Pakistan (DRAP) became the Global Antimicrobial Surveillance System's (GLASS) Focal Point for Antimicrobial Consumption (AMC) Surveillance in 2022. DRAP collaborates with national and international stakeholders to monitor antimicrobial consumption and report data on the GLASS platform.

Several factors contribute to AMR, including behavioural factors such as self-medication and overuse of antimicrobial agents by patients, lack of treatment guidelines, frequent switching of antibiotics and non-adherence to dosage regimens fostering "Superbugs". Inappropriate antimicrobial use in critical and non-critical infections renders severe cases untreatable. In the veterinary sector, antibiotics are overused in the form of growth promoters and feed premixes (prophylactic use). Consuming animal products with residual antimicrobials increases microbial exposure, fueling resistance. In healthcare, inadequate infection control results in critical and resistant hospital-acquired infections. Over-prescription, driven by the absence of guidelines, worsens AMR. Substandard medicines pose quality and health risks, while environmental exposure amplifies resistance.

Key actions have been taken to address these issues. National Infection Prevention and Control (IPC) guidelines have been published, but implementation remains a challenge. The publication of antibiograms and the development of antimicrobial stewardship programs aim to guide healthcare professionals in prescribing effective medicines and reducing overuse. Provincial governments and administrative territories have Drug (Sales) Rules to regulate the sale of antimicrobials but implementation remains a challenge. Strategies to ban the use of antimicrobials as growth promoters and in feed premixes are being devised.

To combat AMR effectively, ongoing efforts include the publication of up-to-date treatment guidelines based on national AMR data, raising awareness, and counselling patients on the importance of following standard treatment regimens. Implementing these measures will contribute to the global fight against AMR, ensuring the effectiveness of antimicrobial agents and safeguarding public health.





Proceedings of 3rd meeting of Pharmacovigilance Risk Assessment Expert Committee (PRAEC)

The 3rd meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held on the 8th of September, 2023 in the Drug Regulatory Authority of Pakistan (DRAP). The meeting was Chaired by Brig(R). Dr. Akbar Waheed, Professor of Pharmacology, Islamic International Medical College, Islamabad and Co-Chaired By Dr. Obaidullah, Head of the National Pharmacovigilance Centre (NPC)/ Director, Division of Pharmacy Services. The committee discussed nine cases of reliance on the safety review reports issued by Reference Regulatory Authorities and so far the NPC has issued six safety alerts through its website.

Furthermore, following the 2nd meeting decision, Provincial Pharmacovigilance Focal persons viz. Sardar Shabbir Ahmed, Senior Drugs Inspector and Focal Person Pharmacovigilance, Islamabad, Mst. Nusrat Rehman, Director, Pharmacovigilance, Directorate of Drugs Control, Punjab, Lahore Punjab and Mst. Aqsa Iftikhar, Dr Shabana Junejo, the Focal Person of Pharmacovigilance, Sindh and Mr Fazal Haq, the Focal Person of Pharmacovigilance Khyber Pakhtunkhwa attended the meeting and apprised the PRAEC about pharmacovigilance activities in their provinces. Dr. Obaidullah, Head of the National Pharmacovigilance Centre briefed about the WHO's recent visit about NRA's assessment of the Global benchmarking Tool and shared the findings of the WHO team regarding pharmacovigilance activities in the country.

PRAEC decided to approach provincial health departments for the nomination of relevant focal persons by health departments on priority with more focus on capacity building and provision of resources to pharmacovigilance teams working in the provinces. PRAEC decided to adopt VigiFlow for adverse events collection at all healthcare levels in provinces and a pilot project for the adoption of VigiFlow will be initiated. After successful implementation, and provision of training, the VigiFlow logins will be extended to all healthcare establishments nationwide. The NPC will coordinate provincial-level centres, emphasizing ADR reporting awareness in public and private healthcare.

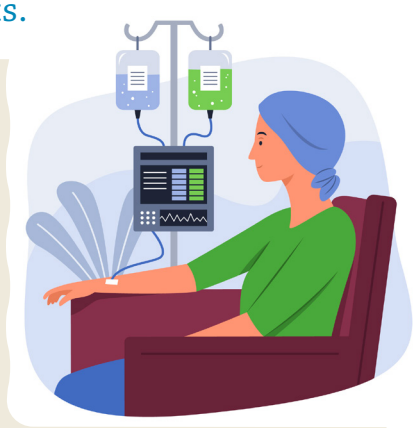
Likewise, the PRAEC deliberated matters related to reports of antibiotic therapeutic inefficacy and the menace of antimicrobial resistance. The committee advised the Pharmacy Services Division to take various measures including drafting a comprehensive proposal for antimicrobial consumption surveillance, antibiotic stewardship program by healthcare establishments, notification of AWaRe list classification and amendment of Drug Sale Rules by relevant health departments for sale on prescription as per international practices including sale of antibiotic, and integrating antibiotics into a risk-based post-marketing surveillance plan by the QA&LT Division, DRAP. The committee also suggested coordinating with the National Institute of Health (NIH) to explore developing antibiograms for various areas/cities.

International Safety Alerts Discussed in 3rd PRAEC Meeting

1. **Fluoropyrimidines:** Risk of potentially life-threatening toxicity in di-hydropyrimidine dehydrogenase (DPD) deficient patients.
2. **Risk of kidney damage with oral anticoagulants**
3. **Moderna and Pfizer COVID-19 Vaccines:** Risk of heavy menstrual bleeding.
4. **Moderna and Pfizer COVID-19 Vaccines:** Risk of myocarditis and pericarditis
5. **Cephalosporins:** Risk of seizures
6. **Third-Generation Aromatase Inhibitors:** Risk of tendon disorders.
7. **Terlipressin:** Risks of respiratory failure, sepsis.
8. **Gemifloxacin:** Risk of Genotoxicity
9. **Codeine with Ibuprofen:** Risks of serious renal and gastrointestinal harms.

International Safety Alerts

Risk of potentially life-threatening toxicity with Fluorouracil and Capecitabine in Di-hydropyrimidine Dehydrogenase (DPD) deficient patients.



The Therapeutic Goods Administration (TGA) of Australia and the Medicine and Health Product Agency (MHRA) of the United Kingdom (UK) issued warnings in September 2022 and October 2020 about fluorouracil, capecitabine, and flucytosine, highlighting severe toxicity risks in patients with partial di-hydropyrimidine dehydrogenase (DPD) deficiency. While these drugs were previously contraindicated for complete DPD deficiency, adverse events suggested toxicity in partial DPD deficiency. Likewise, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency (EMA) in March 2020 also recommended DPD testing before fluorouracil injection/infusion, as lack of DPD enzyme can lead to life-threatening reactions. Complete DPD deficiency patients should avoid these drugs, and reduced starting doses are advised for partial deficiency. The Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the DRAP discussed the case in its 2nd meeting and co-opted oncology experts to assess DPD deficiency testing for Fluorouracil and Capecitabine. In its 3rd meeting held in Sep 2023, based on expert comments, the PRAEC decided to update contraindications for complete DPD deficiency and enhance warnings, emphasizing testing importance before treatment initiation. It also recommended a reduced starting dose for partial DPD deficiency, coupled with increased toxicity monitoring.

Fluorouracil is indicated alone or in combination with other medicines to treat various cancers such as malignant tumours, particularly of the breast, colon or rectum. Also, it is applied to the skin for actinic keratosis and dermal warts. The recommendations are related to system fluorouracil not topical. **Capecitabine** is indicated for the treatment of certain types of colon, colorectal, oesophagogastric and breast cancer.

Patients with a history of DPD deficiency, complete or partial, should notify healthcare professionals. Prompt reporting of fluoropyrimidines-related toxicity (e.g., stomatitis, diarrhoea, mucosal inflammation, neutropenia, neurotoxicity) is essential. **Healthcare professionals** are warned of increased severe toxicity risk in patients with complete or partial DPD deficiency using 5-fluorouracil (intravenous) and capecitabine. They should avoid treating known complete DPD deficiency patients with these drugs and consider a reduced starting dose for partial DPD deficiency. Monitoring for toxicity, especially during the first treatment cycle or after a dose increase, is recommended.

Risk of tendon disorders with 3rd Generation Aromatase Inhibitors

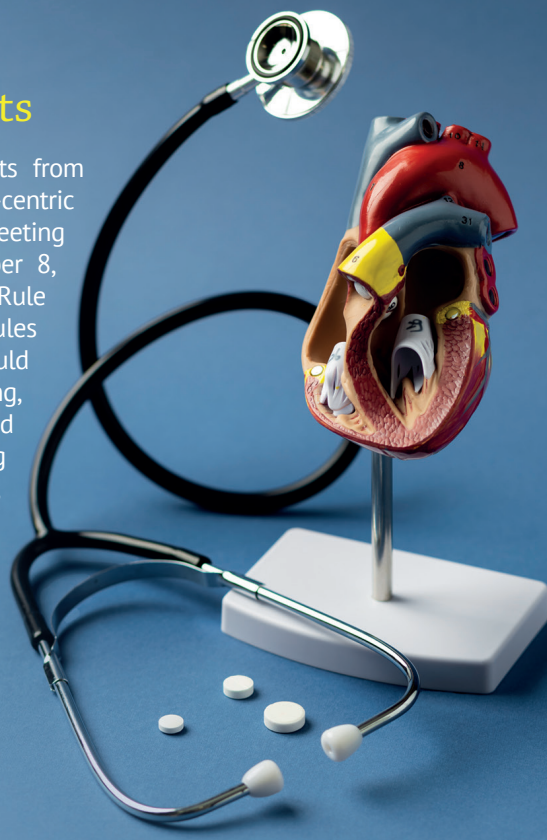
In January 2023, Health Canada announced the update of safety information for 3rd-generation aromatase inhibitors (anastrozole, exemestane, and letrozole) to include the risk of tendon disorders. This decision followed the EMA's inclusion of tendonitis and tendon rupture risks in letrozole safety information. Health Canada is collaborating with manufacturers to update the Canadian Product Monographs. The review considered reports of tendonitis and tenosynovitis in five randomized controlled trials and 25 case reports, suggesting a likely link between third-generation aromatase inhibitors and tendonitis/tenosynovitis, with an uncertain link to tendon rupture. In its 3rd meeting on 8th September 2023, PRAEC-DRAP decided, under Rule 10(1)(h)(iv) of Pharmacovigilance Rules 2022, that registration holders should update prescribing information to include tendon disorders in the warning and precaution section and adverse drug reactions.

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

Patients on third-generation aromatase inhibitors (anastrozole, exemestane, letrozole) should promptly notify healthcare professionals of joint symptoms. **Treating physicians** should monitor for adverse reactions, as these inhibitors are associated with tendonitis and tenosynovitis based on randomized controlled trials. Tendon rupture is a potential risk, with tendonitis and tenosynovitis uncommon and tendon rupture rare.

Risk of Kidney damage with oral Anticoagulants

In June 2023, the TGA of Australia added a warning about serious kidney damage to the prescribing information for all oral anticoagulants given orally, citing Anticoagulant-related nephropathy (ARN) as a rare but serious adverse event. The TGA's investigation, prompted by reports of ARN mainly from overseas, and in this regard consulted the Advisory Committee on Medicines (ACM), which endorsed a class-wide warning for oral anticoagulants, citing documented cases with warfarin and emerging evidence for others. ACM exempted parenteral anticoagulants from the warning due to their hospital-centric and short-duration use. In the 3rd meeting of PRAEC-DRAP held on September 8, 2023, it was decided, under Rule 10(1)(h)(iv) of Pharmacovigilance Rules 2022, that registration holders should include ARN information, monitoring, and evaluation in the warning and precaution section of prescribing information of oral anticoagulants, and also to list as an adverse drug reaction of unknown frequency.



Oral anticoagulants are widely used to prevent and treat thromboembolic conditions and include apixaban, rivaroxaban and warfarin etc. Anticoagulants, sometimes called blood thinners, reduce the blood's natural ability to clot. This alert does not apply to parenteral anticoagulants.

Patients on oral anticoagulants are advised to consult their doctor for any concerns, emphasizing not to discontinue medication without consulting first. Patients are urged to contact their doctor if they experience signs like high blood pressure, reduced urine, blood in urine, or swelling, indicating potential kidney issues. **Healthcare professionals** are alerted to the importance of early detection and intervention in ARN. Despite its rarity and likely underdiagnosis due to infrequent kidney biopsies, professionals are advised to discuss ARN risks with patients. Close monitoring, including renal testing, is recommended, especially for those with excessive anticoagulation or experiencing haematuria.

Risk of serious Renal and Gastrointestinal harms with Codeine plus Ibuprofen drug combination

In September 2022, the European Medicines Agency's PRAC committee recommended updating the product information for codeine with ibuprofen combinations to include a warning about serious harms, especially death, when taken for extended periods or at higher than recommended doses. The PRAC identified cases of renal, gastrointestinal, and metabolic toxicities linked to abuse and dependence on these combinations, some resulting in fatalities. Higher-than-recommended doses or prolonged use were found to potentially cause kidney damage leading to renal tubular acidosis and hypokalaemia. The PRAC suggested that these combination medicines, available without prescription in some countries, should have prescription-only status to minimize harm from abuse and dependence. Therefore, in the 3rd meeting of PRAEC-DRAP, it was decided according to Rule 10(1)(h)(iv) of Pharmacovigilance Rules, 2022, that registration holders of Codeine with Ibuprofen combination in Pakistan should include information about serious harms and specify renal tubular acidosis and hypokalaemia as adverse drug reactions in the product labelling.

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

Patients are informed that the use of codeine with ibuprofen as directed by a doctor is crucial to avoid dependence, abuse, and potentially fatal overdose. Exceeding recommended duration or doses poses serious risks to the stomach, gut, kidneys, and potassium levels. Patients should watch for signs of dependency or addiction, such as prolonged use, increased dosage, non-medical reasons, unsuccessful attempts to quit, or withdrawal effects and consult their doctors or pharmacists. **Healthcare professionals** are informed that extended use of high-dose ibuprofen, especially with codeine, may lead to severe hypokalaemia and renal tubular acidosis. Increased risk arises from potential codeine dependence. Watch for signs like reduced consciousness and weakness. Consider ibuprofen-induced renal tubular acidosis in cases of unexplained hypokalaemia and metabolic acidosis.

Risk of seizures with Cephalosporins

Health Canada, in January 2023, updated cephalosporin product safety information to include the risk of seizures for certain formulations. Triggered by a US FDA update on cefazolin, the review assessed 84 seizure cases, finding 13 probably linked and 62 possibly linked to cephalosporin use. Three cases were unlikely to be linked, and six cases were inconclusive. Health Canada concluded a potential link, pledging collaboration with manufacturers to update product monographs. In March 2023, New Zealand's Medsafe recommended consistent messaging on cephalosporin-induced neurotoxicity, citing risks such as encephalopathy and seizures. Neurotoxicity symptoms may manifest as convulsive or non-convulsive seizures, typically appearing within days of treatment initiation and resolving upon discontinuation. Renal impairment, inadequate dosage adjustments, older age, underlying CNS disorders, and high intravenous doses pose additional risk factors for cephalosporin-induced neurotoxicity. Therefore, in the 3rd meeting of PRAEC-DRAP, it was decided, under Rule 10(1)(h)(iv) of the Pharmacovigilance Rules, 2022, that registration holders for all cephalosporins in Pakistan should include seizure/neurotoxicity information in the warning and precaution, as well as the adverse drug reaction sections of the prescribing information/label.

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

Patients should follow the prescribed antibiotic regimen, and notify their healthcare provider promptly about any signs of seizures/neurotoxicity. **Healthcare professionals** are informed that Cefazolin for Injection may pose a seizure risk, especially in those with renal issues or other risk factors such as older age, CNS disorders, and high intravenous doses. Cease cephalosporin antibiotic use if seizures occur; adjust dosage for renal impairment. Maintain anticonvulsant therapy in patients with known seizure disorders.

Risk of Respiratory failure and sepsis with Terlipressin

In March 2023, the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) announced alignment with the European Medicines Agency's (EMA) recommendations prompted by the CONFIRM trial, indicating the need for new measures to mitigate respiratory failure and sepsis risks associated with terlipressin in type 1 hepatorenal syndrome patients. The trial revealed higher-than-known frequencies of fatal respiratory failure and increased sepsis risk. Earlier, EMA's Pharmacovigilance Risk Assessment Committee, in September 2022, proposed measures following its review of CONFIRM trial data, noting elevated risks in terlipressin-treated patients. The study indicated a higher respiratory failure rate (11%) than previously reported, along with 7% sepsis occurrence. New precautions advise against terlipressin use in patients with advanced liver or kidney conditions. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed these measures on November 10, 2022. Additionally, the US FDA's Terlipressin label includes a Boxed Warning on respiratory failure. In the 3rd PRAEC-DRAP meeting, it was decided under Rule 10 (1) (h) (iv) of Pharmacovigilance Rules, 2022, that terlipressin use for type 1 hepatorenal syndrome (HRS-1) requires strict monitoring for respiratory failure and sepsis. Registration holders should include warnings about avoiding terlipressin in advanced liver or kidney conditions and advise pre-treatment for breathing issues. A boxed warning was recommended.

Terlipressin is a synthetic pituitary hormone used for bleeding oesophagal varices and emergency treatment of type 1 hepatorenal syndrome. The provided advice doesn't apply to its use for bleeding oesophagal varices.

Patients using terlipressin for type 1 hepatorenal syndrome should be aware of an increased risk of respiratory failure and a new risk of sepsis. Any concerns should be discussed with healthcare professionals. **Doctors** should carefully assess benefits and risks, particularly for patients with severe renal or hepatic impairment, monitoring closely during treatment. This advice doesn't apply to terlipressin use for bleeding oesophagal varices. Patients with breathing problems should be treated before starting terlipressin, and continuous infusion may be considered to reduce severe side effects. Monitoring for respiratory failure and infection is recommended during and after treatment.

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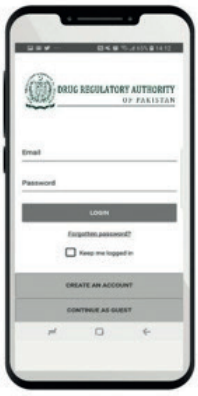
5. Tap `Open`
6. Select a region, in this case **Pakistan**. Sometimes it selects automatically depending on the settings you already have on your phone



7. Click `continue as guest" or "create an account"
8. Report suspected adverse reactions to medicines that have been used

National Pharmacovigilance Centre
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