DRUG REGULATORY AUTHORITY OF PAKISTAN
NATIONAL PHARMACOVIGILANCE CENTRE

PHARMACOVIGILANCE NEWSLETTER

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The purpose of this newsletter is to disseminate the regulatory safety information prepared in light of decisions taken by National Pharmacovigilance Centre, DRAP and other regulatory authorities of the world. Healthcare professionals should acquaint themselves with new information to ensure medication safety.

Vigilance Field Visit of World Health Organization.

A team from World Health Organization (WHO) visited Pakistan for formal benchmarking of the National Regulatory System of the DRAP from 2nd to 12th of May, 2023. A total of nine regulatory functions including pharmacovigilance were assessed during the visit as per the global benchmarking tool to check the World Listed Authority level of the DRAP. Formal benchmarking of pharmacovigilance was conducted at the National Pharmacovigilance Centre, Division of Pharmacy Services, DRAP and Provincial Pharmacovigilance Centre of Punjab to check the overall functioning of pharmacovigilance system in the country.

> "DRAP has pledged to be a model regulatory agency in the region at par with international standards and hopefully, we will achieve this soon. DRAP is also grateful to the WHO for their continuous support for the regulatory system strengthening of Pakistan."
>
> **Asim Rauf**
> Chief Executive Officer, DRAP

The Benchmarking & Visits were conducted at the Following Sites.

- National Pharmacovigilance Centre
- Directorate of Drugs Control, Punjab
- Holy Family Hospital
- CDA-G9 Vaccination Centre

Similarly, a field visit was also conducted at Holy Family Hospital, Rawalpindi and CDA-G9 Vaccination Centre, Islamabad. The purpose was to check the mechanism of collecting, assessing and reporting adverse drug reactions and adverse events following immunization with medicines and vaccines to the Punjab Pharmacovigilance centre and Federal Directorate of Immunization.

Evolution of National Pharmacovigilance System.

The journey of post-market safety surveillance was started by getting associate membership of the World Health Organization Programme for International Drugs Monitoring (WHO-PIDM) in 1994. The activities of Pharmacovigilance were supervised by the Research and Development section of the Drug Control Administration (DCA).

After the establishment of Drug Regulatory Authority of Pakistan (DRAP) under the DRAP Act, of 2012, the Division of Pharmacy Services was given the mandate of developing pharmacovigilance centers and promotion of safety monitoring of therapeutic goods. Accordingly, the National Pharmacovigilance Centre (NPC) was established under the Division of Pharmacy Services in 2017, which started monitoring the adverse drug reactions (ADRs) associated with the use of therapeutic goods across the country in order to prevent harm to patients. The NPC also started coordination with provincial health departments, public health programmes, and registration holders of therapeutic goods for the establishment of their pharmacovigilance centres and regular submission of pharmacovigilance data to the National Centre.

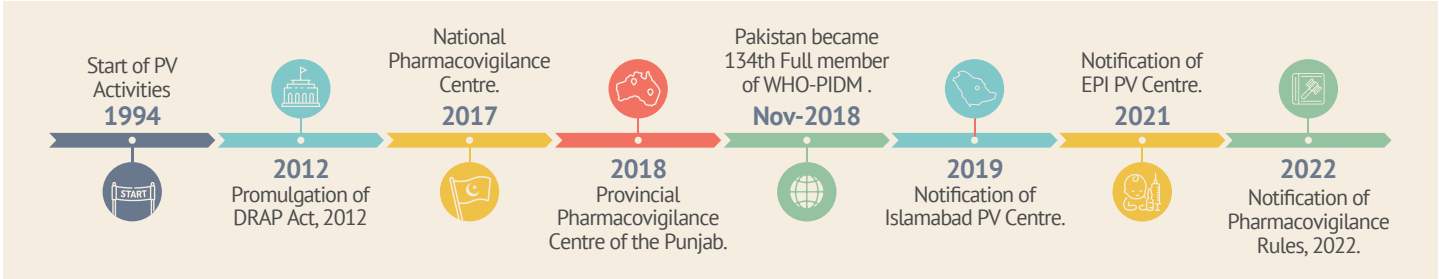
With the endeavours of NPC and through coordination with Uppsala Monitoring Centre and WHO, Pakistan became the 134th full member of WHO-PIDM in 2018. At present, there are two regional/provincial pharmacovigilance centres of NPC viz. the Punjab and Islamabad Pharmacovigilance centres and the centre of the Federal Directorate of Immunization (FDI) which are integrated into the National database (VigiFlow). Moreover, NPC is pursuing other provinces for the establishment of their pharmacovigilance centres and regular submission of adverse events data accordingly.

The NPC has developed guidelines for healthcare professionals, patients, registration holders, public health programmes and provincial health departments on the collection, assessment and reporting of pharmacovigilance data to the NPC. Similarly, the DRAP has statutory notified Pharmacovigilance Rules, 2022 which define the legal responsibilities of each stakeholder in Pakistan. Under these Rules, Pharmacovigilance Risk Assessment Expert Committee (PRAEC) has been notified in June, 2022 and started working as well.

> "The National Pharmacovigilance Centre is mandated to ensure the safety of therapeutic goods in Pakistan as per Pharmacovigilance Rules, 2022. The Centre is striving hard to build a robust pharmacovigilance system in the country and all stackholders have a pivotal role in this regard."
>
> **Dr Obaidullah,**
> Director, Division of Pharmacy Services, DRAP.
> Head of National Pharmacovigilance Centre.

The NPC has different internationally harmonized tools for the collection of adverse events from healthcare professionals and patients such as the Med Vigilance E Reporting System, Med Safety Mobile Application, through yellow reporting form, email, telephone etc. The data from all the pharmacovigilance stakeholders in Pakistan is collected or entered in the National database, validated and properly assessed and transferred to a global database i.e. VigiBase of UMC. The NPC also detect signals in the National Database and along with cases of reports of stringent regulatory authorities present these cases before the PRAEC for its recommendations. Afterwards, the NPC Uploads the information through safety alerts on its website for information of healthcare professionals and patients and communicate the decision to stakeholders.

The NPC encourages healthcare professionals and patients to report adverse events associated with therapeutic goods through the abovementioned channels. Reporting adverse reactions, healthcare professionals help to provide more information about drugs and therapeutic goods, which will ultimately help to make them safer for all and in this way, contribute in ensuring the safety of therapeutic goods. Reporting suspected side effect thus offer an opportunity to identify and further investigate previously unknown or poorly described adverse reaction and helps in continuous monitoring of the safety of the therapeutic good.



Meetings of the Pharmacovigilance Risk Assessment Expert Committee

1st Meeting

The 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee was held at DRAP on the 12th October 2022. The meeting was Chaired by Brigadier Retd Dr Akbar Waheed, Professor, Islamic International Medical College, Rawalpindi and Co-Chaired by Dr Noor Muhammad Shah, Director of Division of Pharmacy Services & Head of National Pharmacovigilance Centre along with experts from universities and hospitals. The committee discussed two cases of local signals and eight cases of reliance on the report of stringent regulatory agencies and made recommendations in this regard.

1st Meeting

DOMESTIC CASES

1. Anaphylactic Reaction with Diclofenac Sodium.
2. Infusion-related hypersensitivity reactions with Remdesivir.

RELIANCE CASES

3. Clozapine: risk of serious bowel complications
4. Iodinated contrast media: risk of hypothyroidism
5. Remdesivir: risk of sinus bradycardia
6. Atezolizumab: risk of SCARs
7. Metformin and reduced vitamin B12 levels
8. Pregabalin: risk of major congenital malformations
9. Interaction between hydroxychloroquine or chloroquine, and macrolide.
10. Hydroxyethyl-starch infusion: risk of kidney injury and death.

2nd Meeting

DOMESTIC CASES

1. Hypersensitivity Reactions with Pegaspargase

RELIANCE CASES

2. Dental problems with Buprenorphine.
3. Benzodiazepines: Risk of Abuse, Dependence and Withdrawal.
4. Fluoropyrimidines: Risk of life-threatening toxicity in DPD deficient patients.
5. JAK inhibitors: Risk of heart-related events, blood clots, cancer & death.
6. Zolpidem: Risk of complex sleep behaviours.
7. Finasteride: Potential risk of suicidal ideation/thoughts & self-injury.
8. Pholcodine: Potential risk of developing anaphylactic reactions to neuromuscular blocking agents (NMBA)

2nd Meeting

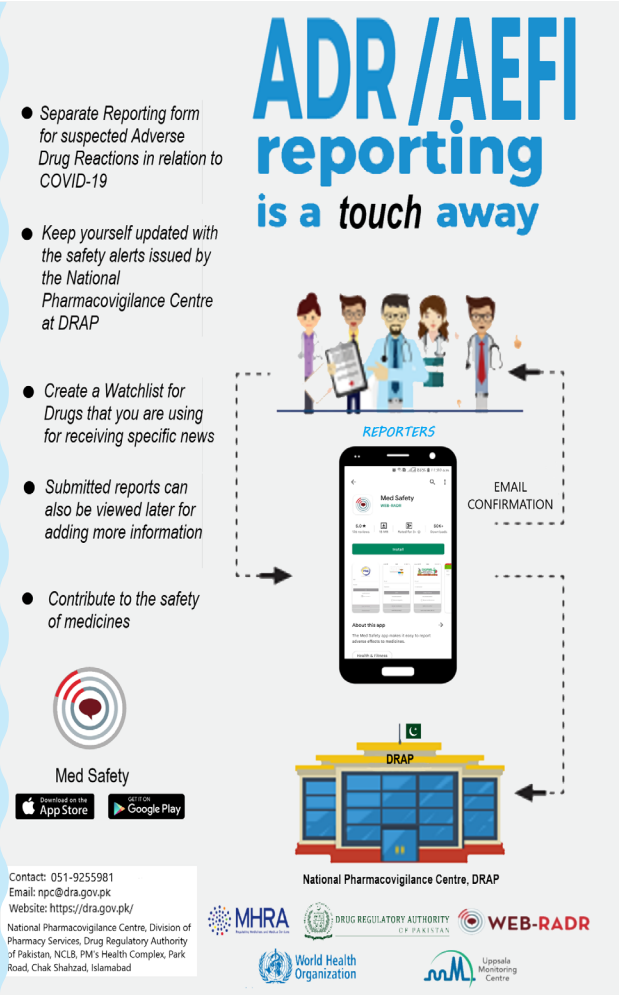
The 2nd meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) was held on 7th March 2023 in the Committee Room of the Drug Regulatory Authority of Pakistan (DRAP). The meeting was Chaired by Brigadier Retd. Dr. Akbar Waheed, Professor of Pharmacology, Islamic International Medical College and Co-Chaired By Dr Obaidullah, Head of the National Pharmacovigilance Centre (NPC) and Director, Division of Pharmacy Services.

The committee discussed one case of domestic signal and seven cases of reliance on the reports of stringent regulatory authorities. Further, the committee adopted a list of reference regulatory authorities, regional bodies and international organizations for reliance in the context of pharmacovigilance decisions in Pakistan. It was also decided that in the next meeting, focal persons of provincial pharmacovigilance centres/ health departments will be invited to attend the meeting and brief the committee about the steps taken at the provincial level for the promotion of pharmacovigilance.

Reporting of Adverse Events with Therapeutic Goods.

Why to Report?

Any new medicine that is developed undergoes trials and testing to determine that it is safe and effective for patients. But this research is limited as it is carried out in a small sample of the population. Certain individual characteristics also vary which affect how the medicine performs in our body. These effects can be positive or negative and therefore sometimes can result in adverse drug reactions. Sometimes associated diseases, using other medication or any other behavioural factor can also result in negative effects of a medicine. To gather this kind of information about medicines and to take appropriate measures of preventing harm to other patients, the National Pharmacovigilance Centre has been established under the Drug Regulatory Authority of Pakistan that aims to ensure that medicines are safe for all. The National Centre collects reports from provincial pharmacovigilance centres, pharmaceutical companies and public health programmes as well as from patients and healthcare professionals. The National Pharmacovigilance Centre would like to encourage patients and healthcare professionals to report adverse events with the use of medicines through available channels. By reporting you can help to provide more information about medicines, which will ultimately help to make them safer and in this way, you may contribute to ensuring the safety of the medicines. For detailed information please visit our website.



What to report ? *(fill these four)*

1. Information on the person reporting so we can follow up for extra information if needed;
2. Information about the patient;
3. At least one medicine that you suspect caused the adverse reaction; and
4. At least one Reaction.

How to Report?

If you are a patient/caregiver:	If you are a doctor, pharmacist, nurse or any other healthcare professional:
• *Med vigilance e-reporting link* • Med safety app • Phone: +92-51-9255981	• *Med vigilance e-reporting link* • Med Safety App • *Yellow reporting form*

Note: Keep in mind that it is sufficient if you have reported through one of the above.

Picture Gallery

Domestic Safety Issues

"Pakistan is a country of 240 million people with four provinces, territories of Islamabad Capital and Gilgit-Baltistan, and a state of Azad Jammu and Kashmir."

The National Pharmacovigilance Centre (NPC) is working under the Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP). It receives cases of Adverse Drug Reactions (ADRs) and Adverse Events Following Immunization (AEFIs) across the country from patients, healthcare professionals, Provincial Pharmacovigilance Centres, Federal Directorate of Immunization (FDI) and registration holders. Based on these locally reported cases, the NPC detects and validates signals and presents these before the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the DRAP for its advice on the matter. The PRAEC discusses domestic cases in its meetings. After the decisions of the committee, the NPC communicates the recommendations to the concerned Boards/Divisions of the DRAP and issues safety alerts on the DRAP website. Domestic safety issues are of prime importance for healthcare professionals in Pakistan as they reflect the local safety profile of the drug.

Risk of Anaphylactic Reaction/Anaphylactic Shock with Diclofenac Sodium Injection

The National Pharmacovigilance Centre (NPC), Drug Regulatory Authority of Pakistan (DRAP), received two cases of anaphylactic reaction with the administration of the Diclofenac Sodium injection (75mg/3ml IM). The cases were reported by Clinical Pharmacy and Pharmacovigilance Officers (CPPOs) from public hospitals in Punjab. The injections were used for wound pain and backache, with one patient having a history of asthma. Symptoms included pruritus, erythema, sweating, fainting, shortness of breath, wheezing, and low blood pressure. The cases were discussed in the 10th meeting of the Adverse Drug Reaction Scrutiny Committee (ADRSC) of the Directorate of Drugs Control Punjab which recommended reporting them to DRAP for investigation and updating the prescribing information/label of Diclofenac Sodium with warning signs of anaphylactic reactions. The NPC-DRAP carried out a further thorough assessment confirming the signal of anaphylactic reactions associated with Diclofenac Sodium. The confirmation was based on the approved labels from the US FDA and SmPC of the Medicine and Health Products Regulatory Agency (MHRA), UK along with published research articles. Disproportionality analysis in VigiLyze also indicated a potential association. In response, the Pharmacovigilance Risk Assessment Expert Committee in its 1st meeting decided, after careful deliberation, to update the prescribing information, safety specifications, and label of the Diclofenac Sodium injection. The updates include information about anaphylactic reactions/shock & contraindications in patients with a history of asthma, urticaria, or allergic-type reactions to aspirin or other NSAIDs.

Intramuscular Diclofenac Sodium effectively treats acute pain conditions such as renal colic, arthritis exacerbations, back pain, gout, trauma, fractures, and postoperative pain. It is an NSAID with anti-inflammatory, analgesic, and antipyretic effects. The mechanism involves inhibiting prostaglandin synthesis through the COX-1 and COX-2 pathways.

Reference:

Safety Alerts on the DRAP website.

Rare anaphylactic reactions may occur with diclofenac sodium injection. **Patients** with a history of asthma, urticaria, or previous reactions to diclofenac/aspirin/NSAIDs should consult their doctor. **Healthcare professionals** should be aware of the risk, discontinue diclofenac if anaphylaxis occurs, and avoid its use in patients with asthma, urticaria, or previous allergic reactions to aspirin/NSAIDs

Risk of Infusion-Related Hypersensitivity Reactions with Remdesivir

National Pharmacovigilance Centre-DRAP received three serious adverse drug reaction reports with Inj Remdesivir (100mg/20ml) used for COVID-19 Pneumonia. Tachycardia, dyspnea, chills, and pyrexia occurred immediately after intravenous administration. A causality assessment of the reports suggested a possible relationship with drug intake. Quality testing was carried out which shows the product is of standard quality. The signal was supported by US-FDA and MHRA-UK labels/ SmPC. Disproportionality analysis in VigiLyze indicated a potential association with infusion-related hypersensitivity reactions. The Pharmacovigilance Risk Assessment Expert Committee of the DRAP in its 1st meeting decided to update the prescribing information/label, by including warnings about hypersensitivity reactions. Educational training for healthcare professionals and patient monitoring was also recommended.

Remdesivir is indicated for the treatment of COVID-19 in adults and pediatric patients (≥28 days old, weighing ≥3 kg) with positive SARS-CoV-2 viral testing. It is used in hospitalized or non-hospitalized patients with mild-to-moderate COVID-19 at high risk of severe disease or hospitalization.

Reference: *Safety Alerts on the DRAP website.*

Remdesivir injection may cause hypersensitivity reactions, including infusion-related reactions. **Patients** should contact their doctor if they experience symptoms such as low/high blood pressure, rapid/slow heart rate, difficulty breathing, rash, nausea, or fever after receiving the injection. **Healthcare professionals** should consider slower infusion rates (up to 120 minutes) to prevent symptoms. Patients should be observed during and after infusion, and if a significant hypersensitivity reaction occurs, the administration of Remdesivir should be stopped immediately and appropriate treatment initiated.

Hypersensitivity Reactions with Pegaspargase (Peg L Asparaginase)

The National Pharmacovigilance Centre-DRAP received six cases of hypersensitivity reactions with Pegaspargase used in children with Acute Lymphoid Leukemia (ALL). Reactions included lip swelling, nausea, rash, vomiting, tongue swelling, itching, shivering, red eyes, and abdominal pain, occurring within one day of Pegaspargase administration (3750IU). The drug was withdrawn in most cases, and all patients recovered. Causality assessment confirmed a possible relationship with the drug, supported by regulatory labels of MHRA and US-FDA and research articles on hypersensitivity reactions. Disproportionality analysis in VigiLyze also indicated a significant association with hypersensitivity.

Following detailed deliberation, the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the NPC-DRAP in its 2nd meeting decided to update the prescribing information, safety specifications or label of Pegaspargase injection. This includes information about hypersensitivity reactions, monitoring, treatment modifications based on reaction grade, and precautions. The registration holder was instructed to implement/introduce an educational training program for healthcare professionals regarding Pegaspargase's preparation, administration, and monitoring. Additionally, ensuring the availability of resuscitation equipment at treatment sites was emphasized.

Pegaspargase (Peg L Asparaginase) is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of pediatric and adult patients with Acute Lymphoid Leukaemia (ALL) and hypersensitivity to native forms of L-asparaginase.

Reference:
Safety Alerts on the DRAP website

Patients are informed that hypersensitivity reactions with Pegaspargase injection can occur during chemotherapy of Acute Lymphoid Leukaemia (ALL). Talk to your doctor if you have a history of hypersensitivity with conventional asparaginase formulations. **Healthcare professionals** are advised of potential hypersensitivity reactions with Pegaspargase, including anaphylaxis. Pre-medication and monitoring are recommended, along with access to resuscitation equipment. Discontinue Pegaspargase in case of serious reactions. Modify treatment based on the severity of the reaction (grade 1: reduce infusion rate by 50%, grade 2: interrupt infusion and treat symptoms, grade 3-4: permanent discontinuation).

International Safety Issues

Stringent regulatory authorities across the world such as the United States Food and Drug Administration, the European Medicines Agency and the Medicine and Health Product Regulatory Agency of the United Kingdom etc. monitor the safety of medicines by collecting adverse events through spontaneous and active surveillance. Based on detected signals followed by evaluation and benefit-risk assessment, these regulatory authorities take regulatory actions to ensure the safety of the medicines in the market of their country. The National Pharmacovigilance Centre, DRAP reviews safety alerts/ information published by medicines regulatory authorities across the world and if deemed appropriate presents these cases before the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the DRAP for reliance on international information. Once agreed upon by the committee, the decisions are implemented in Pakistan.

Risk of Serious Bowel Complications with Clozapine

The TGA of Australia in April, 2022, updated warnings for Clozapine, stating that it can cause severe constipation and slow down bowel function, leading to clozapine-induced gastrointestinal hypomotility. It was informed that untreated constipation can result in serious problems, prompting consumers to monitor bowel changes and contact healthcare professionals if symptoms arise. Similarly, the US-FDA, through a Drug Safety Podcast on January 14, 2022, reinforced a previous warning from February 18, 2020, regarding untreated constipation caused by clozapine. They emphasized the potential for serious bowel complications that may require hospitalization or lead to death if not promptly diagnosed and treated. The risk of serious bowel complications associated with Clozapine was discussed in the 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP). After detailed deliberation, it was decided as part of reliance mechanism to update and strengthen the warning section of product information of Clozapine to include gastrointestinal side effects, including constipation and severe bowel problems.

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

Reference:
Safety Alerts on the DRAP website.

Patients should promptly notify healthcare professionals of symptoms associated with serious bowel problems like nausea, vomiting, or stomach pain. To prevent constipation, patients should increase fibre intake, hydrate adequately, and exercise regularly. **Healthcare professionals** should assess bowel function prior to clozapine initiation, avoid co-prescribing it with other anticholinergic medications, educate patients about the high risk of constipation and potentially life-threatening bowel issues, emphasize the importance of hydration to prevent constipation, and instruct patients to seek immediate medical attention for any difficulties with bowel movements.

Severe Cutaneous Adverse Reactions (SCARs) with Atezolizumab

The National Pharmaceutical Regulatory Agency of Malaysia updated the product information for Atezolizumab (Tecentriq®) in April 2021 to include the risk of severe cutaneous adverse reactions (SCARs). This update was based on the analysis of global safety data, which identified 99 cases of SCARs, with 36 cases confirmed through histopathology or specialist diagnosis. Similarly, the Medicines and Healthcare Products Regulatory Agency (MHRA) also announced in June 2021 that the product information for Atezolizumab has been updated to include information about the risk of SCARs, including Stevens-Johnsons syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). A review of safety data in Europe confirmed the identified risk of SCARs with Atezolizumab. Direct Healthcare Professional Communications (DHPC) was issued by the manufacturers in New Zealand and the European Medicine Agency in November 2020 regarding the risk. SCARs are a group of delayed hypersensitivity reactions, including acute generalized exanthematous pustulosis (AGEP), SJS, TEN, and DRESS. These reactions can be potentially life-threatening, leading to severe and potentially chronic complications. This case was discussed in the 1st meeting of the PRAEC-DRAP in Pakistan. The committee decided to update the prescribing information of Atezolizumab to include the risk of SCARs, including SJS and TEN, as per the Pharmacovigilance Rules. It was also recommended for registration holders to issue direct healthcare professional communication on this matter.

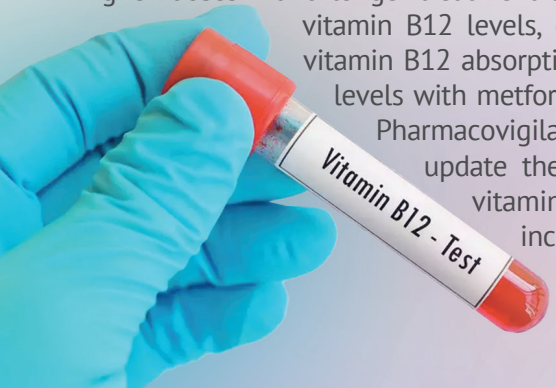
Atezolizumab is an immunostimulatory drug indicated to treat non-small cell lung cancer, small cell lung cancer, hepatocellular carcinoma, urothelial carcinoma and triple-negative breast cancer.

Reference:
Safety Alerts on the DRAP website.

Patients using Atezolizumab should watch for severe skin reactions and seek immediate medical help. **Healthcare professionals** should monitor patients for signs of severe skin reactions, exclude other causes, and refer suspected cases to specialists. In confirmed cases of Stevens-Johnsons Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or grade 4 severe cutaneous adverse reactions (SCARs), treatment with Atezolizumab should be permanently stopped.

Risk of Reduced Vitamin B12 Level with Metformin and Metformin-Containing Medicines

The Medicine and Healthcare Products Regulatory Agency (MHRA) in June, 2022 announced that decreased vitamin B12 levels or deficiency is now considered a common side effect of metformin treatment. This update was based on a review of Glucophage (Metformin) within Europe with input from the MHRA. The product information for metformin-containing medicines, including fixed-dose combination products, was updated to reflect this information. Vitamin B12 deficiency may affect 1 in 10 people taking metformin. The risk of this side effect increases with higher doses and longer treatment duration, as well as in patients with existing risk factors such as low baseline vitamin B12 levels, gastrointestinal disorders, certain diets, concomitant medications that impair vitamin B12 absorption, and genetic predisposition to deficiency. The risk of reduced vitamin B12 levels with metformin and metformin-containing medicines was discussed in 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee of the DRAP. The PRAEC decided to update the prescribing information for metformin and related medications to include vitamin B12 deficiency as an adverse drug reaction. The risk of this reaction increases with higher metformin doses, longer treatment duration, and in patients with risk factors for vitamin B12 deficiency.



Metformin is a medicine authorized to treat type 2 diabetes mellitus and to help prevent type 2 diabetes in patients at high risk of developing it.

Reference: *Safety Alerts on the DRAP website*

Patients with low vitamin B12 levels, gastrointestinal disorders, autoimmune conditions, or genetic predisposition to deficiency should consult their healthcare professionals during metformin treatment. Metformin commonly reduces vitamin B12 levels, increasing the risk of deficiency. **Healthcare professionals** should monitor vitamin B12 levels, test if deficiency is suspected, and consider periodic monitoring for patients with risk factors.

Risk of Hypothyroidism in Babies & Young Children with ICM Injections

The United States Food and Drug Administration (US-FDA) in March, 2022 approved a new warning regarding the use of iodinated contrast media (ICM) injections and monitoring recommendations for children 3 years or younger. The warning highlights the risk of an underactive thyroid or a temporary decrease in thyroid hormone levels associated with ICM injections through an artery or vein. Newborns, especially premature ones, and children with underlying conditions such as heart issues may be at higher risk. The FDA's decision was based on six new research studies that demonstrated a significant risk of hypothyroidism in infants and young children exposed to ICM. Previously, the Medicines and Medical Devices Safety Authority (Medsafe) of New Zealand also requested updates to the data sheets of iodine-containing contrast agents (ICAs) to address the risk of hypothyroidism, particularly in neonates. In Pakistan, the issue was discussed in 1st meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the National Pharmacovigilance Centre (NPC). After careful deliberation, the PRAEC decided to update the warning and precaution section of the prescribing information of all ICMs used for radiological purposes, to inform about the risks of underactive thyroid and a temporary decrease in thyroid hormone levels in children 3 years or younger, including newborns and those with underlying conditions like heart issues.

ICM injections are drugs containing iodine that are given to patients to enhance the ability to see blood vessels, organs, and tissues on medical images such as X-rays or computed tomography (CT) scans, thus helping healthcare professionals to diagnose potential problems. Examples include iohexol (Omnipaque), iopromide (Ultravist) and iodixanol (Visipaque 2) etc.

Reference:
Safety Alerts on the DRAP website.

Parents and caregivers of children under 3 years receiving ICM injections should consult healthcare professionals for more information. Newborns, those with low birth weight, prematurity, heart conditions, or who were admitted to ICUs are at a higher risk of developing underactive thyroid or a temporary decrease in thyroid hormone levels. **Healthcare professionals** should monitor patients from birth to 3 years for hypothyroidism or temporary thyroid hormone level decrease following ICM exposure. Evaluating thyroid function within 3 weeks is advised, particularly in neonates and children with certain conditions. Detected thyroid dysfunction should be treated and monitored as necessary to prevent cognitive and developmental disabilities. Newborns, with low birth weight, premature birth, or cardiac conditions requiring intensive care are at increased risk. Likewise, patients undergoing invasive cardiac procedures are at the greatest risk due to high contrast doses. Close monitoring is necessary for these high-risk pediatric patients.

Risk of Sinus Bradycardia with Remdesivir

In August 2021, Health Canada announced its collaboration with the manufacturer of Remdesivir to update the product information with a warning regarding the potential risk of sinus bradycardia. This decision was based on Health Canada's assessment of case reports found in their database and literature, which indicated a possible link between the use of Remdesivir and the risk of sinus bradycardia. Previously, in June 2021, the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended a revision to the product information for Remdesivir, adding sinus bradycardia as an adverse drug reaction. The PRAC's decision was based on their review of rare cases of bradycardia associated with Remdesivir treatment, data from clinical trials, and scientific literature. Most instances of sinus bradycardia resolved within a few days after discontinuing Remdesivir. Sinus bradycardia is a condition where the heart beats slower than normal, which may be rarely accompanied by symptoms including dizziness, tiredness, shortness of breath, and chest discomfort.

Remdesivir is indicated for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with positive results of direct SARS-CoV-2 viral testing, who are: hospitalized, or not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

Reference: *Safety Alerts on the DRAP website.*

Patients are advised to monitor their symptoms for sinus bradycardia and accordingly inform their healthcare professionals. **Healthcare professionals** are informed about the new update, therefore, they should monitor patients receiving Remdesivir for sinus bradycardia and accordingly treat the patients as appropriate.

Major Congenital Malformations with Pregabalin

The UK's Medicine and Healthcare Products Regulatory Agency (MHRA) in April, 2022 announced that the product information for pregabalin will be updated due to a study suggesting a slight increase in the risk of major congenital malformations if used during pregnancy. The Nordic study showed a higher prevalence of malformations in babies exposed to pregabalin in the first trimester. The MHRA concluded its review that the use of pregabalin during the first trimester may slightly increase the risk of malformations.

The Health Products Regulatory Authority (HPRA) of Ireland also recommended updating product information for pregabalin and other anti-epileptic drugs based on risks associated with in-utero exposure. Product information of pregabalin continues to advise that effective contraception should be used during treatment, and pregabalin use in pregnancy should be avoided unless necessary.

The risk of major congenital malformations with Pregabalin was discussed in 1st meeting of the PRAEC, DRAP which decided to update the prescribing information of Pregabalin based on a new study, stating that it may slightly increase the risk of major congenital malformations if used during pregnancy. The updated information will also include advice on effective contraception during treatment in pregnancy.

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

Reference: Safety Alerts on the DRAP website.

Patients should consult their doctors before starting Pregabalin treatment to discuss the potential benefits and risks, especially in their specific case. They should also discuss the use of appropriate contraception methods to prevent pregnancy during Pregabalin treatment. **Healthcare professionals** should inform patients about the potential risks to an unborn baby and the importance of using effective contraception. Pregabalin should generally be avoided during pregnancy unless absolutely necessary and the benefits outweigh the risks. If Pregabalin must be used during pregnancy, the lowest effective dose should be prescribed

Hydroxychloroquine or Chloroquine with Macrolide Antibiotics

The MHRA in February, 2022 announced that the product information for hydroxychloroquine, chloroquine, and macrolide antibiotics will be updated to include the increased risk of cardiovascular events and mortality when hydroxychloroquine or chloroquine is taken with a macrolide antibiotic. A retrospective study showed that combining azithromycin with hydroxychloroquine in rheumatoid arthritis patients is associated with a higher risk of cardiovascular events and mortality. The revised information will include warnings and advice on these risks for hydroxychloroquine and systemic azithromycin as well as chloroquine and other systemic macrolides such as clarithromycin or erythromycin. Topical macrolide products used for conjunctivitis or acne are not affected.

The product information for hydroxychloroquine and chloroquine already contains warnings about cardiomyopathy and QT interval prolongation. The study suggested that the combined effects of hydroxychloroquine and azithromycin on the QT interval or other cardiotoxic effects may have contributed to the observed events.

The PRAEC-DRAP in its 1st meeting discussed the risk of cardiovascular events associated with the co-administration and interaction between hydroxychloroquine or chloroquine and macrolide antibiotics. It was decided to update the prescribing information (warning and interaction sections) of hydroxychloroquine, chloroquine, and macrolide antibiotics to include information about the increased risk of cardiovascular events and cardiovascular mortality when hydroxychloroquine or chloroquine is taken with a macrolide antibiotic.

Hydroxychloroquine is indicated for the treatment of rheumatoid arthritis, systemic lupus erythematosus, and dermatological conditions aggravated by sunlight. **Chloroquine** is indicated for malaria prophylaxis or treatment and other indications. **Macrolide** antibiotics such as erythromycin, clarithromycin and azithromycin are used to manage and treat various bacterial infections like pneumonia, sinusitis, pharyngitis and tonsillitis etc.

Reference: Safety Alerts on the DRAP website.

Patients are advised that taking macrolide antibiotics together with hydroxychloroquine or chloroquine may increase the risk of heart-related side effects. If they experience heart-related symptoms, they should seek urgent medical help. **Healthcare professionals** should carefully assess the benefits and risks before prescribing systemic azithromycin or other macrolide antibiotics to patients using hydroxychloroquine or chloroquine. Caution should be exercised in patients with risk factors for cardiac events.

Kidney Injury & Death due to Hydroxyethyl-Starch Solutions for Infusion

The European Medicine Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) in February 2022 recommended suspending the market authorization of hydroxyethyl-starch (HES) solutions for infusion in the European Union. These solutions are used as an additional treatment for plasma volume replacement after sudden blood loss. Previous safety reviews in 2013 and 2018 led to restrictions and measures to minimize the risk of kidney injury and death in certain patients. Despite these restrictions, a recent study showed that HES solutions for infusion were still being used outside the recommended guidelines, posing serious risks to certain patient groups. Consequently, the PRAC advised suspending the marketing authorizations for HES solutions, and the European Commission confirmed this decision on May 24, 2022. The PRAEC-DRAP discussed the risk of kidney injury and death associated with HES solutions for infusion in Pakistan. After thorough deliberation, the PRAEC-DRAP recommended suspending the registration of HES solutions in Pakistan, subject to the availability of alternative treatment options, in accordance with the Pharmacovigilance Rules, 2022.

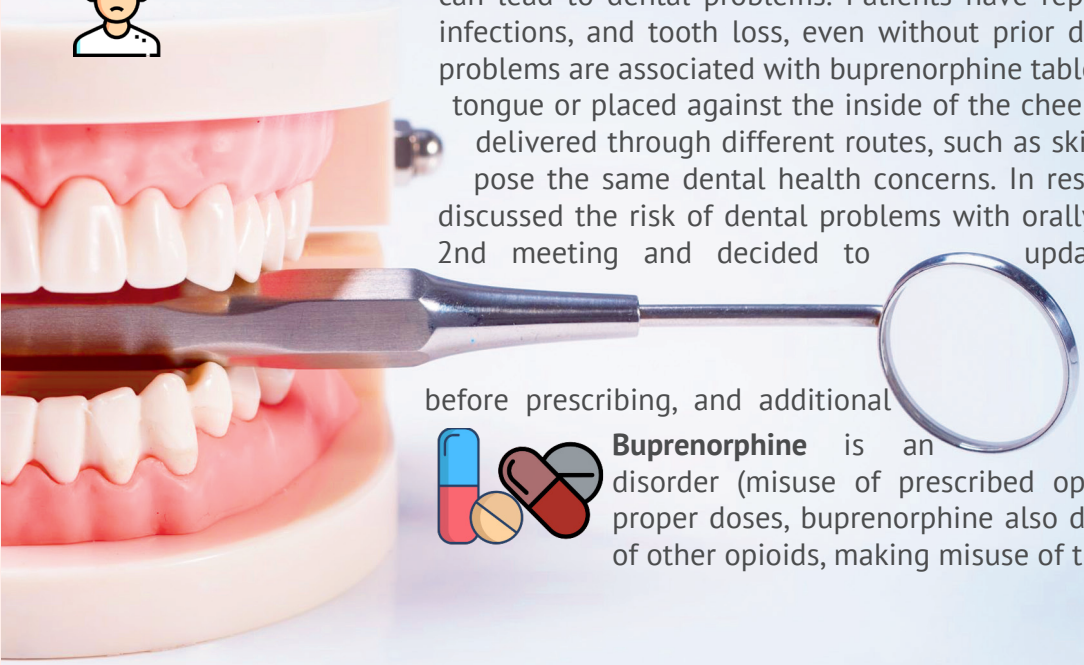
Hydroxyethyl-Starch solutions for infusion are indicated as an addition to other treatments for plasma volume replacement following acute (sudden) blood loss.

Reference: *Safety Alerts on the DRAP website.*

Patients should be aware that the National Pharmacovigilance Centre, DRAP, is working towards suspending the registration of HES solutions for infusion in Pakistan. It is advisable to consult with your doctor before starting treatment with these solutions, as alternative options are available. Similarly, **healthcare professionals** are reminded that alternative solutions for infusion, suitable for plasma volume replacement are readily available in the Pakistani market and should be considered as the preferred treatment in such cases.

Dental problems with orally dissolved Buprenorphine

The US-FDA issued a warning on January 12, 2022, stating that medicines containing buprenorphine can lead to dental problems. Patients have reported tooth decay, cavities, oral infections, and tooth loss, even without prior dental issues. Specifically, dental problems are associated with buprenorphine tablets and films dissolved under the tongue or placed against the inside of the cheek. Other buprenorphine products delivered through different routes, such as skin patches and injections, do not pose the same dental health concerns. In response, the PRAEC of NPC-DRAP discussed the risk of dental problems with orally dissolved buprenorphine in its 2nd meeting and decided to update the product information for these medicines, including information about the dental risks, patient assessment before prescribing, and additional precautions after use.



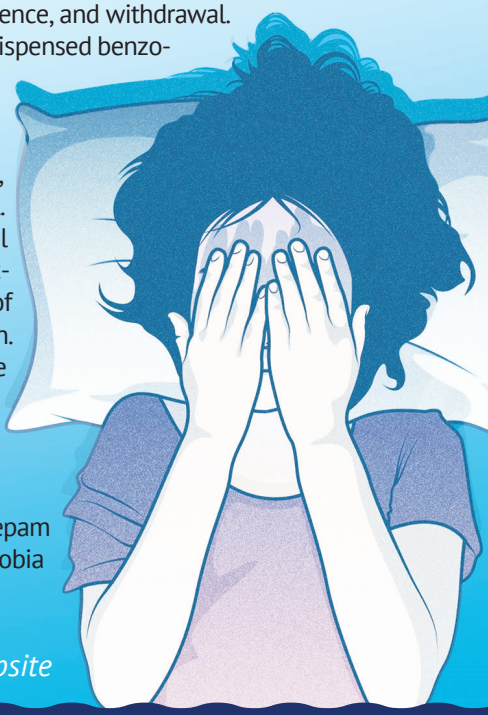
Buprenorphine is an opioid used to treat opioid use disorder (misuse of prescribed opioid medications) and pain. At proper doses, buprenorphine also decreases the pleasurable effects of other opioids, making misuse of them less appealing.

Reference: *Safety Alerts on the DRAP website.*

Patients must continue taking prescribed buprenorphine medication to avoid withdrawal symptoms. To minimize dental issues, patients should rinse their mouth with water and wait at least 1 hour before brushing their teeth after dissolving buprenorphine. **Healthcare professionals** should review patients' oral health history before prescribing oral buprenorphine. They should also educate patients about potential dental problems and stress the importance of rinsing with water than swallowing, and waiting at least 1 hour before brushing their teeth after medication dissolution.

Risk of Abuse, Dependence and Withdrawal with Benzodiazepines

In June 2022, the Medsafe of New Zealand issued a reminder to prescribers about the updated product information for benzodiazepines, highlighting the potential risks of abuse, dependence, and withdrawal. Dispensing data showed that diazepam and lorazepam were the most commonly dispensed benzodiazepines, indicating frequent and/or long-term use. Medsafe advised healthcare professionals to counsel patients about the risks of benzodiazepines, regularly review the need for treatment, and gradually taper the medication to reduce withdrawal risk. In September 2020, the United States FDA required boxed warnings for all benzodiazepines, including information about abuse, misuse, addiction, physical dependence, and withdrawal. Combining benzodiazepines with other substances can result in overdose or death, and physical dependence can occur even with prescribed use. Abrupt discontinuation or rapid dosage reduction can lead to life-threatening withdrawal reactions, including seizures. Concurrent use of benzodiazepines and opioids can cause severe sedation, respiratory depression, coma, and death. These medications should be prescribed together only when alternative treatment options are inadequate. The PRAEC-DRAP also discussed the risks of benzodiazepines in its 2nd meeting and decided to update prescribing information to include warnings about abuse, misuse, addiction, and withdrawal. A boxed warning will be created as per the FDA format.



Benzodiazepines such as Diazepam, Alprazolam, Clonazepam, Lorazepam, Bromazepam etc. are indicated to treat generalized anxiety disorders, insomnia, seizures, social phobia and panic disorders.

Reference: Safety Alerts on the DRAP website

Patients should inform healthcare professionals about all prescription and over-the-counter medications, including alcohol being used and should take benzodiazepines as prescribed. If discontinuation is necessary, a healthcare professional should be consulted to create a gradual tapering plan. Immediate medical attention should be sought if withdrawal symptoms occur. **Healthcare professionals** should assess the risk of abuse, misuse, and addiction before prescribing benzodiazepines and regularly review the need for treatment. Caution is advised when prescribing to patients with a history of substance abuse. Benzodiazepines should be used short-term for anxiety or insomnia (2-4 weeks). Prolonged use may lead to dependence, especially with higher doses or in high-risk patients. Abrupt discontinuation or rapid dose reduction can cause severe withdrawal reactions, including convulsions and psychosis. Patients should also be advised to consult their doctor before reducing or stopping treatment, as an individualized tapering schedule is necessary.

Risk of complex sleep behaviours with Zolpidem

In July 2022, the MHLW and PMDA of Japan announced the need for revised product information on triazolam, zolpidem, zopiclone, and eszopiclone, highlighting the risk of abnormal behavior as parasomnia. Triazolam, zolpidem, and zopiclone are contraindicated in patients with a history of abnormal behavior, while eszopiclone requires careful administration. These drugs can increase the risk of serious self harm/other injuries or accidents. The US-FDA previously warned about similar risks in April 2019, requiring a Boxed Warning and contraindication for eszopiclone, zaleplon, and zolpidem due to complex sleep behaviors resulting in injuries and even deaths. These behaviors can occur with or without alcohol or other sedating medications. In the 2nd meeting of the PRAEC, the risk of complex sleep behaviours with Zolpidem was discussed, and it was decided that the prescribing information of zolpidem-containing drugs should be updated. This includes adding information about complex sleep behaviour in the warning and precaution sections, contraindications for patients with a history of such behaviours & creating a boxed warning as per the FDA.

Zolpidem tartrate is indicated for the short-term treatment of insomnia characterized by difficulties with sleep initiation.

Reference: *Safety Alerts on the DRAP website.*

Patients experiencing complex sleep behaviours or memory loss while taking Zolpidem should stop using it and consult their healthcare professionals. **Healthcare professionals** should inquire about past parasomnia-related behaviours before prescribing Zolpidem and avoid prescribing it to patients with a history of such behaviours. Patients should be informed about the rare but serious risks and advised to discontinue the medication if such behaviour occur.

Serious heart-events, blood clots, cancer & death with Tofacitinib.

In September 2022, Health Canada updated the safety information for JAK inhibitors (e.g., tofacitinib, baricitinib, upadacitinib) to include the risk of heart problems, blood clots, cancer, and death. The decision was based on a 2019 clinical study linking tofacitinib to higher risks, as well as interim findings from a 2021 study on baricitinib. Health Canada suggested a class effect among JAK inhibitors, extending the risks to other drugs like upadacitinib, abrocitinib, ruxolitinib, and fedratinib. In October 2021, the UK's MHRA advised against tofacitinib use in patients over 65, smokers, and those with cardiovascular or malignancy risk factors, unless there are no suitable alternatives. This decision resulted from a safety trial revealing increased risks of heart attacks and certain cancers. Japan's MHLW and PMDA also revised tofacitinib package inserts in October 2021, emphasizing the risk of cardiovascular events. The US FDA issued a Drug Safety Communication on September 1, 2021, reporting an increased risk of heart-related events, cancer, blood clots, and death with Xeljanz (tofacitinib) used for arthritis and ulcerative colitis. The trial indicated higher risks even with lower doses, prompting revisions to the Boxed Warning. In June 2021, the PRAC of the EMA recommended an update for tofacitinib, advising its use only in certain patient populations with cardiovascular and malignancy risk factors based on a study involving patients aged 50 or older. In summary, regulatory agencies have updated safety information for JAK inhibitors, primarily tofacitinib, due to concerns about heart problems, blood clots, cancer, and death. Specific recommendations were provided for patients with certain risk factors. The NPC-DRAP previously issued Safety Alert No. 16 regarding the risk of heart-related events, cancer, blood clots, and death with Tofacitinib. Considering updates from other regulatory authorities, the case was submitted to the PRAEC. In the 2nd meeting, the PRAEC decided to update the prescribing information of Tofacitinib medicines, including warnings about heart attack, stroke, cancer, blood clots, and death, and to create a Boxed warning as per the FDA format.

Tofacitinib treats chronic inflammatory conditions like rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis. It works by reducing immune system activity, which is involved in these conditions.

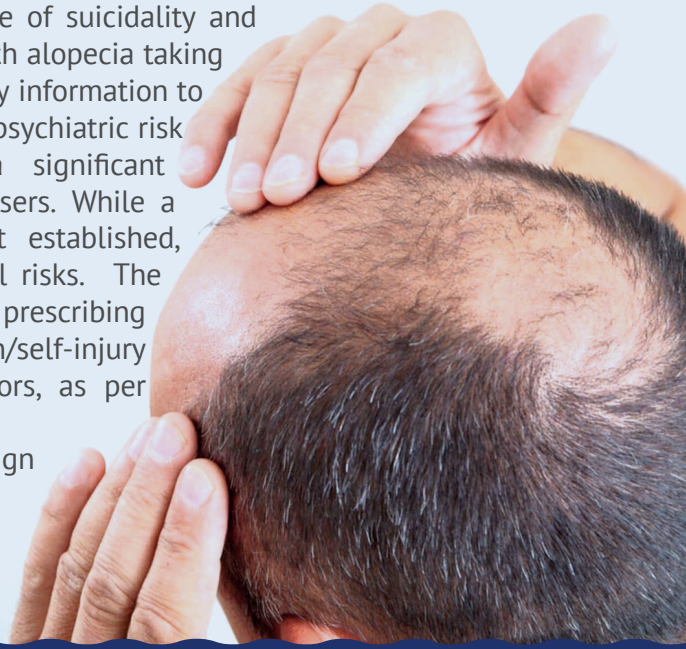
Reference:
Safety Alerts on the DRAP website.

Patients taking Xeljanz should inform their healthcare professionals about their smoking history, heart problems, stroke, or blood clot history, as these may increase the risk of serious complications. They should immediately seek emergency help if they experience symptoms such as chest discomfort, shortness of breath, weakness, slurred speech, or leg pain. Xeljanz is associated with an increased risk of certain cancers, and patients should notify their healthcare professional if they have symptoms like swollen lymph nodes, fatigue, fever, persistent cough, or unexplained weight loss. **Healthcare professionals** should carefully assess the benefits and risks of Xeljanz, particularly in patients with specific risk factors or existing malignancies.

Suicidal ideation/thoughts & self-injury with Finasteride.

The Health Sciences Authority (HSA) of Singapore in August 2022 and Health Canada in January, 2023 have raised concerns about the potential risk of suicidal ideation with the use of finasteride. A pharmacovigilance study showed a higher incidence of suicidality and psychological adverse events in younger patients with alopecia taking finasteride. Health Canada is working on updating product safety information to include stronger warning statements and patient screening for psychiatric risk factors. The recent Vigilyze statistics also identified a significant disproportionality signal for suicidal ideation in finasteride users. While a definitive link between finasteride and suicide risk is not established, cautionary measures are being taken to address the potential risks. The PRAEC, NPC-DRAP recommended an update of finasteride's prescribing information to strengthen warnings about suicidal ideation/self-injury risks and include patient screening for psychiatric risk factors, as per Pharmacovigilance Rules, 2022.

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



Reference: Safety Alerts on the DRAP website.

Patients should promptly notify their doctors if they experience mood changes, depression, or, less commonly, suicidal thoughts or self-injury while taking finasteride. **Healthcare professionals** should be aware of the potential risk of psychological adverse events and consider it when evaluating the benefits and risks of prescribing finasteride. Patients should be advised by healthcare professionals to seek immediate medical attention if they develop such thoughts.

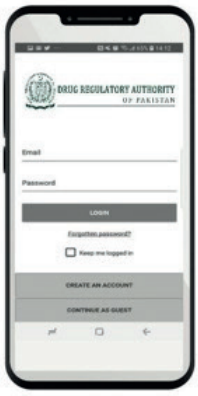
How to download the Med Safety App:

GET IT ON Google Play

Download on the App Store

1. Open the Play Store (Android) or the App Store (iOS)

2. Search for `Med Safety`
3. Tap the `Med Safety` Icon
4. Tap to `install` to the download the App
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

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