STORAGE
Store below 30°C in a dry place, protect from light.
To be dispensed on the prescription of a registered medical practitioner only.
Keep out of the reach of children.

PRESENTATION
QUETAP 25 mg Tablets are supplied in Alu Alu Blister pack of 3 X10's.
QUETAP 100 mg Tablets are supplied in Alu Alu Blister pack of 3 X10's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر خشک جگہ پر رکھیں، روشنی سے بچائیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Platinum Pharmaceuticals (Pvt.) Ltd.
A 20,North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

QAR No.AW15-0025

Quetap

(Quetiapine Fumarate)
Film Coated Tablet

کیوٹیپ
(کیوٹیاپین فیومارییٹ)

COMPOSITION

Each film coated tablet contains:
Quetiapine (As fumarate)..... 25 mg
(Platinum Specs)
Product Complies Platinum Specs.

Each film coated tablet contains:
Quetiapine (As fumarate)..... 100 mg
(Platinum Specs)
Product Complies Platinum Specs.

DESCRIPTION
Quetiapine fumarate is a psychotropic agent of the dibenzothiazepine derivatives class.

CLINICAL PHARMACOLOGY
Mechanism of Action
The exact mechanism of action of (QUETAP) is unknown. However, it has been proposed that the efficacy of (QUETAP) in schizophrenia and its mood stabilizing properties in bipolar mania are mediated through a combination of dopamine type$_2$ (D_2) and serotonin type$_2$ ($5HT_2$) antagonisms. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of QUETAP.
QUETAP's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.
QUETAP's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacodynamics
QUETAP is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$, dopamine D_1 and D_2, histamine H_1 and adrenergic α_1 and α_2 receptors. QUETAP has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors.

Pharmacokinetics
QUETAP fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of Quetiapine is dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption
Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, and C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution
Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*,

quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination
Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major,but inactive, sulfoxide metabolite and in the metabolism of its active metabolite N-desalkyl quetiapine.

Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

INDICATIONS
Quetiapine fumarate is indicated for the treatment of:
1. Schizophrenia.
2. Bipolar Mania.

DOSAGE AND ADMINISTRATION
QUETAP can be taken with or without food

Indication	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia	25 mg twice daily	150-750 mg/day	750 mg/day
Bipolar Mania Monotherapy or as an adjunct to lithium or Divalproex	50 mg twice daily	400 - 800 mg/day	800 mg/day

CONTRAINDICATIONS
Known hypersensitivity to QUETAP or any of its excipients.

ADVERSE REACTIONS
Most common adverse reactions (incidence ≥5% and twice placebo):
Somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, dyspepsia.

DRUG INTERACTIONS
The risks of using QUETAP in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of QUETAP, caution should be used when it is taken in combination with other centrally acting drugs.

Quetiapine exposure is increased by the prototype CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone, etc.) and decreased by the prototype CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, avasimibe, St. John's wort etc.). Dose adjustment of quetiapine will be necessary if it is co-administered with potent CYP3A4 inducers or inhibitors.

Because of its potential for inducing hypotension, QUETAP may enhance the effects of certain antihypertensive agents.
QUETAP may antagonize the effects of levodopa and dopamine agonists.

USE IN SPECIFIC POPULATIONS
Pregnancy: Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Quetiapine was excreted into human milk; a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother's health.

Pediatric Use: Safety and effectiveness of QUETAP in pediatric patients less than 13 years of age with schizophrenia have not been established. Safety and effectiveness of QUETAP in pediatric patients less than 10 years of age with bipolar mania have not been established.

Geriatric Use: Consider a lower starting dose, slower titration and careful monitoring during the initial dosing period in the elderly.

Renal Insufficiency:
Dosage adjustment is not needed in these patients.

Hepatic Impairment: Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed. A low starting dose of 25 mg/day is recommended and the dose may be increased in increments of 25 mg/day - 50 mg/day

WARNINGS AND PRECAUTIONS
• ***Cerebrovascular Adverse Reactions:*** Increased incidence of cerebrovascular adverse events (e.g. stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs.

• ***Neuroleptic Malignant Syndrome (NMS):*** Manage with immediate discontinuation and close monitoring.

• ***Metabolic Changes:*** Atypical antipsychotics have been associated with metabolic changes. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain.

• ***Tardive Dyskinesia:*** Discontinue if clinically appropriate.

• ***Hypotension:*** Use with caution in patients with known cardiovascular or cerebrovascular disease.

• ***Increased Blood Pressure in Children and Adolescents:*** Monitor blood pressure at the beginning of, and periodically during treatment in children and adolescents.

• ***Leukopenia, Neutropenia and Agranulocytosis:*** Monitor complete blood count frequently during the first few months of treatment in patients with a pre-existing low white cell count or a history of leukopenia/neutropenia and discontinue QUETAP at the first sign of a decline in WBC in absence of other causative factors.

• ***Cataracts:*** Lens changes have been observed in patients during long-term QUETAP treatment. Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment.

OVERDOSAGE
In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse reactions or recovered fully from the reported reactions.

Management of Overdosage
In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.