Quto XR

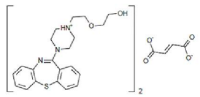
(Quetiapine)

50mg, 150mg,
200mg & 300mg
Tablets

کیوٹوایکس آر
(کیوٹاپاپین)

DESCRIPTION

Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water, it is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is C46 H54 N6 O8 S2 and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Warning:

Increased mortality in elderly patients with dementia-related psychosis; and suicidal thoughts and behaviors. Increased Mortality in Elderly Patients with Dementia-Related Psychosis
•Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Quetiapine fumarate extended-release tablets are not approved for elderly patients with dementia-related psychosis. Suicidal Thoughts and behaviours
•Increased risk of suicidal thoughts and behaviours in children, adolescents and young adults taking antidepressants.
•Monitor for worsening and emergence of suicidal thoughts and behaviours.

CLINICAL PHARMACOLOGY

Pharmacodynamics

QUTO XR is an antagonist at multiple neurotransmitter receptors in the brain: serotonin 5HT1A and 5HT2 (IC50s=717 & 148nM respectively), dopamine D1 and D2 (IC50s=1268 & 329nM respectively), histamine H1 (IC50=30nM), and adrenergic α1 and α2 receptors (IC50s=94 & 271nM, respectively). QUTO XR has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC50s>5000 nM).

The mechanism of action of QUTO XR, as with other drugs having efficacy in the treatment of schizophrenia and acute manic episodes associated with bipolar disorder, is unknown. However, it has been proposed that this drugs efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D2) and serotonin type 2(5HT2) antagonism. Antagonism at receptors other than dopamine and 5HT2 with similar receptor affinities may explain some of the other effects of QUTO XR.

QUTO XR antagonism of histamine H1 receptors may explain the somnolence observed with this drug.

QUTO XR antagonism of adrenergic α1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug.The multiple-dose pharmacokinetics of quetiapine are 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, with Cmax 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: Following a single oral dose of 14C 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.

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 iso enzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups:

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary.

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (ClCr=10-30 mL/min/1.73 m2, n=8) had a 25% lower mean oral clearance than normal subjects (ClC=> 80 mL/min/1.73 m2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and Cmax were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population,and dosage adjustment may be needed

Indications and usage

Quetiapine fumarate is an atypical antipsychotic indicated for the treatment of:

- Schizophrenia
- Bipolar I disorder, manic or mixed episodes
- Bipolar disorder, depressive episodes
- Major depressive disorder, adjunctive therapy with antidepressants

Dosage and administration

- Swallow tablets whole and do not split, chew or crush
- Take without food or with a light meal (approx. 300 calories)
- Administer once daily, preferably in the evening
- Geriatric Use: Consider a lower starting dose (50 mg/day), slower titration, and careful monitoring during the initial dosing period in the elderly.
- Hepatic Impairment: Lower starting dose (50 mg/day) and slower titration may be needed

Indication	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia - Adults	300 mg/day	400-800 mg/day	800 mg/day
Schizophrenia - Adolescents (13 to 17 years)	50 mg/day	400-800 mg/day	800 mg/day
Bipolar I Disorder manic or mixed - Acute monotherapy or adjunct to lithium or divalproex-Adults	300 mg/day	400-800 mg/day	800 mg/day
Bipolar I Disorder, manic Acute monotherapy - Children and Adolescents (10 to 17 years)	50 mg/day	400-600 mg/day	600 mg/day
Bipolar Disorder, Depressive Episodes - Adults	50 mg/day	300 mg/day	300 mg/day
Major Depressive Disorder, Adjunctive Therapy with Antidepressants - Adults	50 mg/day	150-300 mg/day	300 mg/day

Contraindications

Known hypersensitivity to quetiapine fumarate extended-release tablets or any components in the formulation.

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 psychosis 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
- Hyperglycemia and Diabetes Mellitus: Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
- Dyslipidemia: Undesirable alterations have been observed in patients treated with atypical antipsychotics. Appropriate clinical monitoring is recommended, including fasting blood lipid testing at the beginning of, and periodically, during treatment
- Weight Gain: Gain in body weight has been observed; clinical monitoring of weight is recommended
- 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 quetiapine fumarate extended-release tablets 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 quetiapine treatment. Lens examination is recommended when starting treatment and at 6-month intervals during chronic treatment

Adverse reactions

Most common adverse reactions (incidence ≥5% and twice placebo):
Adults: somnolence, dry mouth, constipation, dizziness, increased appetite, dyspepsia, weight gain, fatigue, dysarthria, and nasal congestion
Children and Adolescents: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight increased

Drug interactions

- Concomitant use of strong CYP3A4 inhibitors: Reduce quetiapine dose to one sixth when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir)
- Concomitant use of strong CYP3A4 inducers: Increase quetiapine dose up to 5 fold when used in combination with a chronic treatment (more than 7-14 days) of potent CYP3A4 inducers (e.g., phenytoin, rifampin, St. John's wort)
- Discontinuation of strong CYP3A4 inducers: Reduce quetiapine dose by 5 fold within 7-14 days of discontinuation of CYP3A4 inducers

Use in specific populations

- Pregnancy: Limited human data. Based on animal data, may cause fetal harm. Quetiapine should be used only if the potential benefit justifies the potential risk
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother's health

Strengths

Extended-Release Tablets: 50 mg, 150 mg, 200 mg and 300 mg

Dosage: As directed by the Physician.
Instruction: Store below 25ºC. Protect from sunlight and moisture.
Keep all medicines out of the reach of children.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: دوا کو 25ºC سے کم درجہ حرارت پر دھوپ اور نمی سے محفوظ رکھیں۔
تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

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