APO-QUETIAPINE
Quetiapine as Quetiapine Fumarate Tablets 25 mg, 100 mg and 200 mg

PRODUCT DESCRIPTION
25 mg: Peach, round, biconvex, film-coated tablet. Engraved "APO" on one side, "QUE" over "25" on the other side.
100 mg: Yellow, round, biconvex, film-coated tablet. Engraved "APO" on one side, "QUE" over "100" on the other side.
200 mg: White, round, biconvex, film-coated tablet. Engraved "APO" on one side, "QUE" over "200" on the other side.

PHARMACOLOGY
Pharmacodynamics
Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and N-desalkyl quetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. Quetiapine exhibits a higher affinity for serotonin ($5HT_2$) receptors in the brain than it does for dopamine D_1 and D_2 receptors in the brain. Additionally, N-desalkyl quetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and N-desalkyl quetiapine also have high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2-receptor blockade.

Pharmacokinetics
Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is approximately 83% bound to plasma proteins. Steady-state peak molar concentrations of the active metabolite N-desalkyl quetiapine are 35% of that observed for quetiapine. The elimination half-lives of quetiapine and N-desalkyl quetiapine are approximately 7 and 12 hours, respectively.
The pharmacokinetics of quetiapine and N-desalkyl quetiapine are linear across the approved dosing range. The kinetics of quetiapine do not differ between men and women.
The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73m^2) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite N-desalkyl quetiapine is <5% excreted in the urine. Quetiapine is extensively metabolised, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

INDICATION
- Treatment of depressive episodes associated with bipolar disorder.
- Treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct to lithium or divalproex.
- Treatment of schizophrenia.

RECOMMENDED DOSE
Adults:
Schizophrenia: Quetiapine should be administered twice daily, with or without food.
Quetiapine should generally be administered with an initial dose of 25 mg twice daily, with increases in increments of 25-50 mg twice or thrice daily on the 2nd and 3rd day, as tolerated, to a target dose range of 300-400 mg daily by the 4th day, given twice or thrice daily. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for quetiapine would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg twice daily are recommended.
Antipsychotic efficacy was demonstrated in a dose range of 150-750 mg/day in the clinical trials supporting the effectiveness of quetiapine. In a dose-response study, doses >300 mg/day were not demonstrated to be more efficacious than the 300-mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety and efficacy of doses >800 mg/day has not been evaluated in clinical trials.
Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with quetiapine should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients continued on quetiapine, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.
Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of <1 week off quetiapine, titration of quetiapine is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off quetiapine for >1 week, the initial titration schedule should be followed.

Acute Manic Episodes Associated with Bipolar I Disorder: Quetiapine should be administered twice daily, with or without food.
As monotherapy or as adjunct therapy to mood stabilizers (lithium or divalproex), the total daily dose for the first 4 days of therapy is 100 mg (day 1), 200 mg (day 2), 300 mg (day 3) and 400 mg (day 4). Further dosage adjustment up to 800 mg/day by day 6 should be in increments of no greater than 200 mg/day.
The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200-800 mg/day. The usual effective dose range is 400-800 mg/day.

Depressive Episodes Associated with Bipolar Disorder: Quetiapine should be administered once daily at bedtime, with or without food.
Quetiapine should be titrated as follows: 50 mg (day 1), 100 mg (day 2), 200 mg (day 3) and 300 mg (day 4). Quetiapine can be titrated to 400 mg on day 5 and up to 600 mg by day 8.
Antidepressant efficacy was demonstrated with quetiapine at 300 and 600 mg, however, no additional benefit was seen in the 600-mg group.

Elderly: As with other antipsychotics, quetiapine should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on quetiapine 25 mg/day. The dose should be increased daily, in increments of 25-50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Children and Adolescents**:** The safety and efficacy of quetiapine have not been evaluated in children and adolescents.

Renal and Hepatic Impairment: The oral clearance of quetiapine is reduced by approximately 25% in patients with renal or hepatic impairment. Quetiapine is extensively metabolized by the liver and therefore, should be used with caution in patients with known hepatic impairment.
Patients with renal or hepatic impairment should be started on quetiapine 25 mg/day. The dose should be increased daily, in increments of 25-50 mg, to an effective dose.

MODE OF ADMINISTRATION
Oral

CONTRAINDICATION
Contra-indicated in patients who are hypersensitive to any component of this product.

PRECAUTIONS/WARNINGS
Cardiovascular disease
Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.
Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients.
QT Prolongation

As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Seizures

As with other antipsychotics, caution is recommended when treating patients with a history of seizures.

Tardive dyskinesia

As with other antipsychotics, there is a potential for quetiapine to cause tardive dyskinesia after long-term treatment. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia

Quetiapine should be discontinued in patients with a neutrophil count <1.0 X 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 X 10^9/L). Acute withdrawal reactions

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable.

Effects on ability to drive and use machines

Because quetiapine may cause somnolence, patients should be cautioned about operating hazardous machines, including motor vehicles.

Hyperglycemia and Diabetes Mellitus

Hyperglycaemia in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotics use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in the general population. Given this confounders, the relationship between atypical antipsychotic use and hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

DRUG INTERACTIONS

Concomitant use of quetiapine with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of quetiapine may need to be considered if quetiapine is used concomitantly with a hepatic enzyme inducer.

During concomitant administration of drugs which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of quetiapine should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

Hyperglycaemia

Hyperglycaemia or exacerbation of pre-existing diabetes has been reported during treatment with quetiapine. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine should be used with caution in combination with other centrally acting drugs and alcohol.

The pharmacokinetics of lithium was not altered when co-administered with quetiapine.
The pharmacokinetics of valproic acid and quetiapine were not altered to a clinically relevant extent when co-administered as valproate semisodium (also known as divalproex sodium) and quetiapine. Valproate semisodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship.
The pharmacokinetics of quetiapine was not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine.
Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, in a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of quetiapine is 750mg/day for the treatment of schizophrenia and 800mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).
CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). However, caution is recommended when quetiapine is co-administered with potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors).

USE IN PREGNANCY AND LACTATION:
The safety and efficacy of quetiapine during human pregnancy have not been established. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.
The degree to which quetiapine is excreted into human milk is unknown. Women who are breast feeding should therefore be advised to avoid breast feeding while taking quetiapine.
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity, while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalisation.
This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

ADVERSE EFFECTS
The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are somnolence, dizziness, dry mouth, mild asthenia, constipation, tachycardia, orthostatic hypotension, and dyspepsia.
As with other antipsychotics, syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral edema, have been associated with quetiapine.
The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

Blood and lymphatic system disorders	
Common:	Leucopenia
Uncommon:	Eosinophilia
Immune system disorders	
Uncommon:	Hypersensitivity
Very rare:	Anaphylactic reaction
Metabolism and nutritional disorders	
Very rare:	Diabetes Mellitus [1, 6, 16]
Psychiatric disorders	
Common:	Abnormal dreams and nightmares
Nervous system disorders	
Very Common:	Dizziness [1, 5] , somnolence [2]
Common:	Syncope [1, 5] , Extrapyramidal symptoms [1, 15]
Uncommon:	Seizure [1] , Restless leg syndrome, Dysarthria
Cardiac disorders	
Common:	Tachycardia [1, 5]
Eye disorders	
Common:	Vision blurred
Vascular disorders	
Common:	Orthostatic hypotension [1, 5]
Respiratory, thoracic and mediastinal disorders	
Common:	Rhinitis
Gastrointestinal disorders	
Very Common:	Dry mouth
Common:	Constipation, dyspepsia
Uncommon:	Dysphagia [12]
Reproductive system and breast disorders	
Rare:	Priapism
General disorders and administration site conditions	
Very Common:	Withdrawal (discontinuation) symptoms [1, 9]
Common:	Mild asthenia, peripheral oedema
Rare:	Neuroleptic malignant syndrome [1]
Investigations	
Very Common:	Elevations in serum triglyceride levels [10] , elevations in total cholesterol (predominantly LDL cholesterol) [11]
Common:	Weight gain [3] , elevations in serum transaminases (ALT, AST) [4] , decreased neutrophil count [7] , blood glucose increased to hyperglycaemic levels [8, 16]
Uncommon:	Elevations in gamma-GT levels [4] , platelet count decreased [13]
Rare:	Elevations in blood creatine phosphokinase [14]

(1) See 'Precautions/Warning'.
(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.
(3) Occurs predominantly during the early weeks of treatment.
(4) Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine.
(5) As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.
(6) Exacerbation of pre-existing diabetes has been reported in very rare cases.
(7) In placebo-controlled monotherapy trials in patients with a baseline neutrophil count $\geq$ 1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10^9/L was 1.72% in patients treated with quetiapine compared to 0.73% in placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator; patients with a baseline neutrophil count $\geq$1.5 x 10^9/L), the incidence of at least one occurrence of neutrophil count <0.5 x 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo-treated patients and the incidence $\geq$ 0.5 - <1.0 x 10^9/L was 0.75% in patients treated with quetiapine and 0.11% in placebo-treated patients.
(8) Fasting blood glucose $\geq$ 7.0 mmol/L or a non fasting blood glucose $\geq$ 11.1.mmol/L on at least one occasion.
(9) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
(10) Triglycerides $\geq$200 mg/dL ($\geq$2.258 mmol/L) on at least one occasion.
(11) Cholesterol $\geq$240 mg/dL ($\geq$6.2064 mmol/L) on at least one occasion.
(12) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
(13) Platelets $\leq$ 100 x 10^9/L on at least one occasion.
(14) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
(15) See text below.
(16) Calculation of frequency for these ADRs have been taken from post-marketing data only.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported very rarely with the use of neuroleptics and are considered class effects.
Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first two to four weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. Smaller decreases in total T_3 and reverse T_3 were seen only at higher doses. Levels of TBG were unchanged and in general, reciprocal increases in TSH were not observed, with no indication that quetiapine causes clinically relevant hypothyroidism.
Exacerbation of pre-existing diabetes has been reported in very rare cases during quetiapine treatment.
As with other antipsychotics, quetiapine may be associated with weight gain, predominantly during the early weeks of treatment.
Acute withdrawal reactions have been reported.

Respiratory, Thoracic and Mediastinal Disorders:
Atypical antipsychotic drugs such as Quetiapine, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Apo-Quetiapine should be prescribed with caution.

Renal and Urinary Disorders:
Urinary Retention.

SYMPTOMS AND TREATMENT OF OVERDOSE
Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams.
In post-marketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma or QT-prolongation.
In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension.
Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.
Management
There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a

patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.
Close medical supervision and monitoring should be continued until the patient recovers.

AVAILABILITY OF DOSAGE FORMS

Apo-Quetiapine tablets 25 mg, 100 mg and 200 mg will be packaged in HDPE Bottles of 100's.

STORAGE CONDITIONS

Store below 30°C.

MANUFACTURER

Apotex Inc., 150 Signet Drive, Weston Ontario, M9L 1T9 Canada.

DATE OF REVISION

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