769-2024-01

Quetiapine Tablets, USP
11383
2078951
2D CODE

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use QUETIAPINE TABLETS safely and effectively. See full prescribing information for QUETIAPINE TABLETS.

QUETIAPINE tablets, for oral use

Initial U.S. Approval: 1997

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.
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 tablets are not approved for elderly patients with dementia-related psychosis (5.1)**

Suicidal Thoughts and Behaviors
- **Increased risk of suicidal thoughts and behavior in children, adolescents and young adults taking antidepressants (5.2)**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.2)**

INDICATIONS AND USAGE

Quetiapine tablets are an atypical antipsychotic indicated for the treatment of:
- Schizophrenia (1.1)
- Bipolar I disorder manic episodes (1.2)
- Bipolar disorder, depressive episodes (1.2)

DOSAGE AND ADMINISTRATION

Indication	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia-Adults (2.2)	25 mg twice daily	150-750 mg/day	750 mg/day
Schizophrenia-Adolescents (13-17 years) (2.2)	25 mg twice daily	400-800 mg/day	800 mg/day
Bipolar Mania-Adults Monotherapy or as an adjunct to lithium or divalproex (2.2)	50 mg twice daily	400–800 mg/day	800 mg/day
Bipolar Mania-Children and Adolescents (10 -17 years), Monotherapy (2.2)	25 mg twice daily	400-600 mg/day	600 mg/day
Bipolar Depression-Adults (2.2)	50 mg once daily at bedtime	300 mg/day	300 mg/day

- *Geriatric Use:* Consider a lower starting dose (50 mg/day), slower titration and careful monitoring during the initial dosing period in the elderly (2.3, 8.5)
- *Hepatic Impairment:* Lower starting dose (25 mg/day) and slower titration may be needed (2.4, 8.7, 12.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, and 400 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to quetiapine or any components in the formulation. (4)

WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs (5.3)
- *Neuroleptic Malignant Syndrome (NMS):* Manage with immediate discontinuation and close monitoring (5.4)
- *Metabolic Changes:* Atypical antipsychotics have been associated with metabolic changes. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain (5.5)
  - 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 (5.6)
- *Hypotension:* Use with caution in patients with known cardiovascular or cerebrovascular disease (5.7)
- *Increased Blood Pressure in Children and Adolescents:* Monitor blood pressure at the beginning of, and periodically during treatment in children and adolescents (5.8)
- *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 at the first sign of a decline in WBC in absence of other causative factors (5.10)
- *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 (5.11)
- *Anticholinergic (antimuscarinic) Effects:* Use with caution with other anticholinergic drugs and in patients with urinary retention, prostatic hypertrophy, or constipation (5.20)

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5% and twice placebo): Adults: somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, pharyngitis, weight gain, lethargy, ALT increased, dyspepsia (6.1)
- Children and Adolescents: somnolence, dizziness, fatigue, increased appetite, nausea, vomiting, dry mouth, tachycardia, weight increased (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- *Concomitant use of strong CYP3A4 inhibitors:* Reduce quetiapine dose to one sixth when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole, ritonavir) (2.5, 7.1, 12.3)
- *Concomitant use of strong CYP3A4 inducers:* Increase quetiapine dose up to 5 fold when used in combination with a chronic treatment (more than 7 to 14 days) of potent CYP3A4 inducers (e.g., phenytoin, rifampin, St. John's wort) (2.6, 7.1, 12.3)
- *Discontinuation of strong CYP3A4 inducers:* Reduce quetiapine dose by 5 fold within 7 to 14 days of discontinuation of CYP3A4 inducers (2.6, 7.1, 12.3)

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 01/2024

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FULL PRESCRIBING INFORMATION

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 [*see Warnings and Precautions (5.1)*]. Quetiapine tablets are not approved for the treatment of patients with dementia-related psychosis [*see Warnings and Precautions (5.1)*].

Suicidal Thoughts and Behaviors

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [*see Warnings and Precautions (5.2)*].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [*see Warnings and Precautions (5.2)*].

Quetiapine tablets are not approved for use in pediatric patients under ten years of age [*see Use in Specific Populations (8.4)*].

1 INDICATIONS AND USAGE

1.1 Schizophrenia

Quetiapine tablets are indicated for the treatment of schizophrenia. The efficacy of quetiapine tablets in schizophrenia was established in three 6-week trials in adults and one 6-week trial in adolescents (13 to 17 years). The effectiveness of quetiapine tablets for the maintenance treatment of schizophrenia has not been systematically evaluated in controlled clinical trials [*see Clinical Studies (14.1)*].

1.2 Bipolar Disorder

Quetiapine tablets are indicated for the acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex. Efficacy was established in two 12-week monotherapy trials in adults, in one 3-week adjunctive trial in adults, and in one 3-week monotherapy trial in pediatric patients (10 to 17 years) [*see Clinical Studies (14.2)*].

Quetiapine tablets are indicated as monotherapy for the acute treatment of depressive episodes associated with bipolar disorder. Efficacy was established in two 8-week monotherapy trials in adult patients with bipolar I and bipolar II disorder [*see Clinical Studies (14.2)*].

Quetiapine tablets are indicated for the maintenance treatment of bipolar I disorder, as an adjunct to lithium or divalproex. Efficacy was established in two maintenance trials in adults. The effectiveness of quetiapine tablets as monotherapy for the maintenance treatment of bipolar disorder has not been systematically evaluated in controlled clinical trials [*see Clinical Studies (14.2)*].

1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder

Pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for pediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the risks associated with medication treatment. Medication treatment for both pediatric schizophrenia and bipolar I disorder is indicated as part of a total treatment program that often includes psychological, educational and social interventions.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Quetiapine tablets can be taken with or without food.

2.2 Recommended Dosing

The recommended initial dose, titration, dose range and maximum quetiapine tablets dose for each approved indication is displayed in Table 1. After initial dosing, adjustments can be made upwards or downwards, if necessary, depending upon the clinical response and tolerability of the patient [*see Clinical Studies (14.1 and 14.2)*].

Table 1: Recommended Dosing for Quetiapine Tablets

Indication	Initial Dose and Titration	Recommended Dose	Maximum Dose
Schizophrenia-Adults	Day 1: 25 mg twice daily. Increase in increments of 25 mg-50 mg divided two or three times on Days 2 and 3 to range of 300-400 mg by Day 4. Further adjustments can be made in increments of 25 – 50 mg twice a day, in intervals of not less than 2 days.	150-750 mg/day	750 mg/day
Schizophrenia-Adolescents (13-17 years)	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-800 mg/day. Based on response and tolerability, may be administered three times daily.	400-800 mg/day	800 mg/day
Schizophrenia-Maintenance	Not applicable.	400–800 mg/day	800 mg/day
Bipolar Mania- Adults Monotherapy or as an adjunct to lithium or divalproex	Day 1: Twice daily dosing totaling 100 mg. Day 2: Twice daily dosing totaling 200 mg. Day 3: Twice daily dosing totaling 300 mg. Day 4: Twice daily dosing totaling 400 mg. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.	400–800 mg/day	800 mg/day
Bipolar Mania- Children and Adolescents (10 to 17 years), Monotherapy	Day 1: 25 mg twice daily. Day 2: Twice daily dosing totaling 100 mg. Day 3: Twice daily dosing totaling 200 mg. Day 4: Twice daily dosing totaling 300 mg. Day 5: Twice daily dosing totaling 400 mg. Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400-600 mg/day. Based on response and tolerability, may be administered three times daily.	400-600 mg/day	600 mg/ day
Bipolar Depression- Adults	Administer once daily at bedtime. Day 1: 50 mg Day 2: 100 mg Day 3: 200 mg Day 4: 300 mg	300 mg/day	300 mg/day
Bipolar I Disorder Maintenance Therapy-Adults	Administer twice daily totaling 400-800 mg/day as adjunct to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized.	400-800 mg/day	800 mg/day

Maintenance Treatment for Schizophrenia and Bipolar I Disorder

Maintenance Treatment – Patients should be periodically reassessed to determine the need for maintenance treatment and the appropriate dose for such treatment [*see Clinical Studies (14.2)*].

2.3 Dose Modifications in Elderly Patients

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions [*see Clinical Pharmacology (12.3)*]. When indicated, dose escalation should be performed with caution in these patients.

Elderly patients should be started on quetiapine tablets 50 mg/day and the dose can be increased in increments of 50 mg/day depending on the clinical response and tolerability of the individual patient.

2.4 Dose Modifications in Hepatically Impaired Patients

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25 mg/day to 50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

2.5 Dose Modifications when used with CYP3A4 Inhibitors

Quetiapine tablets dose should be reduced to one sixth of original dose when co-medicated with a potent CYP3A4 inhibitor (e.g., ketoconazole, itraconazole, indinavir, ritonavir, nefazodone, etc.). When the CYP3A4 inhibitor is discontinued, the dose of quetiapine tablets should be increased by 6-fold [*see Clinical Pharmacology (12.3) and Drug Interactions (7.1)*].

2.6 Dose Modifications when used with CYP3A4 Inducers

Quetiapine tablets dose should be increased up to 5-fold of the original dose when used in combination with a chronic treatment (e.g., greater than 7 to 14 days) of a potent CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, avasimibe, St. John's wort etc.). The dose should be titrated based on the clinical response and tolerability of the individual patient. When the CYP3A4 inducer is discontinued, the dose of quetiapine tablets should be reduced to the original level within 7 to 14 days [*see Clinical Pharmacology (12.3) and Drug Interactions (7.1)*].

2.7 Re-initiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address re-initiation of treatment, it is recommended that when restarting therapy of patients who have been off quetiapine tablets for more than one-week, the initial dosing schedule should be followed. When restarting patients who have been off quetiapine tablets for less than one-week, gradual dose escalation may not be required and the maintenance dose may be re-initiated.

2.8 Switching from Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to quetiapine tablets, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate quetiapine tablets therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

3 DOSAGE FORMS AND STRENGTHS

- Quetiapine Tablets USP, 25 mg are peach colored, round shaped, biconvex, film-coated tablets debossed with '44' on one side and '1' on the other side
- Quetiapine Tablets USP, 50 mg are white to off white colored, round shaped, biconvex, film-coated tablets debossed with '47' on one side and '1' on the other side.
- Quetiapine Tablets USP, 100 mg are yellow colored, round shaped, biconvex, film-coated tablets debossed with '55' on one side and '1' on the other side.
- Quetiapine Tablets USP, 200 mg are white to off white colored, round shaped, biconvex, film-coated tablets debossed with '56' on one side and '1' on the other side.
- Quetiapine Tablets USP, 300 mg are white to off white colored, capsule shaped, biconvex, film-coated tablets debossed with '45' on one side and '1' on the other side.
- Quetiapine Tablets USP, 400 mg are yellow colored, capsule shaped, biconvex, film-coated tablets debossed with '57' on one side and '1' on the other side.

4 CONTRAINDICATIONS

Hypersensitivity to quetiapine or to any excipients in the quetiapine tablets formulation. Anaphylactic reactions have been reported in patients treated with quetiapine tablets.

5 WARNINGS AND PRECAUTIONS

5.1 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. Analysis of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Quetiapine is not approved for the treatment of patients with dementia-related psychosis [*see Boxed Warning*].

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 2.

Table 2: Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
< 18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for quetiapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, including quetiapine, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Quetiapine is not approved for the treatment of patients with dementia-related psychosis *(see also Boxed Warning and Warnings and Precautions (5.1))*.

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including quetiapine. Rare cases of NMS have been reported with quetiapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

5.5 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile. In some patients, a worsening of more than one of the metabolic parameters of weight, blood glucose, and lipids was observed in clinical studies. Changes in these metabolic profiles should be managed as clinically appropriate.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse reactions is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions 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.

Adults:

Table 3: Fasting Glucose-Proportion of Patients Shifting to ≥ 126 mg/dL in Short-Term (≤ 12 weeks) Placebo-Controlled Studies[1]

Laboratory Analyte	Category Change (At Least Once) from Baseline	Treatment Arm	N	Patients n (%)
Fasting Glucose	Normal to High (< 100 mg/dL to ≥ 126 mg/dL)	Quetiapine	2907	71 (2.4%)
		Placebo	1346	19 (1.4%)
	Borderline to High (≥ 100 mg/dL and < 126 mg/dL to ≥ 126mg/dL)	Quetiapine	572	67 (11.7%)
		Placebo	279	33 (11.8%)

1. Includes quetiapine and quetiapine extended-release data.

In a 24-week trial (active-controlled, 115 patients treated with quetiapine) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at Week 24 the incidence of a post-glucose challenge glucose level ≥200 mg/dL was 1.7% and the incidence of a fasting blood glucose level ≥ 126 mg/dL was 2.6%. The mean change in fasting glucose from baseline was 3.2 mg/dL and mean change in 2-hour glucose from baseline was -1.8 mg/dL for quetiapine.

In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar I disorder maintenance, mean exposure of 213 days for quetiapine (646 patients) and 152 days for placebo (680 patients), the mean change in glucose from baseline was +5.0 mg/dL for quetiapine and –0.05 mg/dL for placebo. The exposure-adjusted rate of any increased blood glucose level (≥ 126 mg/dL) for patients more than 8 hours since a meal (however, some patients may not have been precluded from calorie intake from fluids during fasting period) was 18.0 per 100 patient years for quetiapine (10.7% of patients; n = 556) and 9.5 for placebo per 100 patient years (4.6% of patients; n = 581).

Children and Adolescents:

In a placebo-controlled quetiapine monotherapy study of adolescent patients (13 to 17 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for quetiapine (n = 138) compared to placebo (n = 67) was –0.75 mg/dL versus –1.70 mg/dL. In a placebo-controlled quetiapine monotherapy study of children and adolescent patients (10 to 17 years of age) with bipolar mania (3 weeks duration), the mean change in fasting glucose level for quetiapine (n = 170) compared to placebo (n = 81) was 3.62 mg/dL versus –1.17 mg/dL. No patient in either study with a baseline normal fasting glucose level (< 100 mg/dL) or a baseline borderline fasting glucose level (≥ 100 mg/dL and < 126 mg/dL) had a blood glucose level of ≥ 126 mg/dL.

In a placebo-controlled quetiapine extended-release tablets monotherapy study (8 weeks duration) of children and adolescent patients (10 to 17 years of age) with bipolar depression, in which efficacy was not established, the mean change in fasting glucose levels for quetiapine extended-release tablets (n = 60) compared to placebo (n = 62) was 1.8 mg/dL versus 1.6 mg/dL. In this study, there were no patients in the quetiapine extended-release tablets or placebo-treated groups with a baseline normal fasting glucose level (< 100 mg/dL) that had an increase in blood glucose level > 126 mg/dL. There was one patient in the quetiapine extended-release tablets group with a baseline borderline fasting glucose level (> 100 mg/dL and < 126 mg/dL) who had an increase in blood glucose level of > 126 mg/dL compared to zero patients in the placebo group.

Dyslipidemia

Adults:

Table 4 shows the percentage of adult patients with changes in total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol from baseline by indication in clinical trials with quetiapine.

Table 4: Percentage of Adult Patients with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol, and HDL-Cholesterol from Baseline to Clinically Significant Levels by Indication

Laboratory Analyte	Indication	Treatment Arm	N	Patients n (%)
Total Cholesterol ≥ 240 mg/dL	Schizophrenia[1]	Quetiapine	137	24 (18%)
		Placebo	92	6 (7%)
	Bipolar Depression[2]	Quetiapine	463	41 (9%)
		Placebo	250	15 (6%)
Triglycerides ≥ 200 mg/dL	Schizophrenia[1]	Quetiapine	120	26 (22%)
		Placebo	70	11 (16%)
	Bipolar Depression[2]	Quetiapine	436	59 (14%)
		Placebo	232	20 (9%)
LDL-Cholesterol ≥ 160 mg/dL	Schizophrenia[1]	Quetiapine	na[3]	na[3]
		Placebo	na[3]	na[3]
	Bipolar Depression[2]	Quetiapine	465	29 (6%)
		Placebo	256	12 (5%)
HDL-Cholesterol ≤ 40 mg/dL	Schizophrenia[1]	Quetiapine	na[3]	na[3]
		Placebo	na[3]	na[3]
	Bipolar Depression[2]	Quetiapine	393	56 (14%)
		Placebo	214	29 (14%)

1. 6 weeks duration
2. 8 weeks duration
3. Parameters not measured in the quetiapine tablets registration studies for schizophrenia.

Children and Adolescents:

Table 5 shows the percentage of children and adolescents with changes in total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol from baseline in clinical trials with quetiapine.

Table 5: Percentage of Children and Adolescents with Shifts in Total Cholesterol, Triglycerides, LDL-Cholesterol, and HDL-Cholesterol from Baseline to Clinically Significant Levels

Laboratory Analyte	Indication	Treatment Arm	N	Patients n (%)
Total Cholesterol ≥ 200 mg/dL	Schizophrenia[1]	Quetiapine	107	13 (12%)
		Placebo	56	1 (2%)
	Bipolar Mania[2]	Quetiapine	159	16 (10%)
		Placebo	66	2 (3%)
Triglycerides ≥ 150 mg/dL	Schizophrenia[1]	Quetiapine	103	17 (17%)
		Placebo	51	4 (8%)
	Bipolar Mania[2]	Quetiapine	149	32 (22%)
		Placebo	60	8 (13%)
LDL-Cholesterol ≥ 130 mg/dL	Schizophrenia[1]	Quetiapine	112	4 (4%)
		Placebo	60	1 (2%)
	Bipolar Mania[2]	Quetiapine	169	13 (8%)
		Placebo	74	4 (5%)
HDL-Cholesterol ≤ 40 mg/dL	Schizophrenia[1]	Quetiapine	104	16 (15%)
		Placebo	54	10 (19%)
	Bipolar Mania[2]	Quetiapine	154	16 (10%)
		Placebo	61	4 (7%)

1. 13 to 17 years, 6 weeks duration
2. 10 to 17 years, 3 weeks duration

In a placebo-controlled quetiapine extended-release tablets monotherapy study (8 weeks duration) of children and adolescent patients (10 to 17 years of age) with bipolar depression, in which efficacy was not established, the percentage of children and adolescents with shifts in total cholesterol (≥ 200 mg/dL), triglycerides (≥ 150 mg/dL), LDL-cholesterol (≥ 130 mg/dL) and HDL-cholesterol (≤ 40 mg/dL) from baseline to clinically significant levels were: total cholesterol 8% (7/83) for quetiapine extended-release tablets vs. 6% (5/84) for placebo; triglycerides 28% (22/80) for quetiapine extended-release tablets vs. 9% (7/82) for placebo; LDL-cholesterol 2% (2/86) for quetiapine extended-release tablets vs. 4% (3/85) for placebo and HDL-cholesterol 20% (13/65) for quetiapine extended-release tablets vs. 15% (11/74) for placebo.

Weight Gain

Increases in weight have been observed in clinical trials. Patients receiving quetiapine should receive regular monitoring of weight.

Adults:

In clinical trials with quetiapine the following increases in weight have been reported.

Table 6: Proportion of Patients with Weight Gain ≥ 7% of Body Weight (Adults)

Vital Sign	Indication	Treatment Arm	N	Patients n (%)
Weight Gain ≥ 7% of Body We

Preferred Term	Quetiapine 400 mg (n=95)	Quetiapine 600 mg (n=98)	Placebo (n=90)
Weight Increased	6%	6%	0%
Irritability	3%	5%	1%
Pyrexia	1%	4%	1%
Aggression	1%	3%	0%
Musculoskeletal Stiffness	1%	3%	1%
Accidental Overdose	0%	2%	0%
Acne	3%	2%	0%
Arthralgia	4%	2%	1%
Lethargy	2%	2%	0%
Pallor	1%	2%	0%
Stomach Discomfort	4%	2%	1%
Syncope	2%	2%	0%
Vision Blurred	3%	2%	0%
Constipation	4%	2%	0%
Ear Pain	2%	0%	0%
Paraesthesia	2%	0%	0%
Sinus Congestion	3%	0%	0%
Thirst	2%	0%	0%

1. Somnolence combines adverse reactions terms somnolence and sedation.
2. Tachycardia combines adverse reaction terms tachycardia and sinus tachycardia.

Extrapyramidal Symptoms:
In a short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration), the aggregated incidence of extrapyramidal symptoms was 12.9% (19/147) for quetiapine and 5.3% (4/75) for placebo, though the incidence of the individual adverse reactions (akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration), the aggregated incidence of extrapyramidal symptoms was 3.6% (7/193) or quetiapine and 1.1% (1/90) for placebo.

Table 15 presents a listing of patients with adverse reactions potentially associated with extrapyramidal symptoms in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration).

In Tables 15 to 16 dystonic event included nuchal rigidity, hypertonia, and muscle rigidity; parkinsonism included cogwheel rigidity and tremor; akathisia included akathisia only; dyskinetic event included tardive dyskinesia, dyskinesia, and choreoathetosis; and other extrapyramidal event included restlessness and extrapyramidal disorder.

Table 15: Adverse Reactions Associated with Extrapyramidal Symptoms in the Placebo-Controlled Trial in Adolescent Patients with Schizophrenia (6-week duration)

Preferred Term	Quetiapine 400 mg/day (N=73)		Quetiapine 800 mg/day (N=74)		All Quetiapine (N=147)		Placebo (N=75)	
	n	%	n	%	n	%	n	%
Dystonic event	2	2.7	0	0.0	2	1.4	0	0.0
Parkinsonism	4	5.5	4	5.4	8	5.4	2	2.7
Akathisia	3	4.1	4	5.4	7	4.8	3	4.0
Dyskinetic event	2	2.7	0	0.0	2	1.4	0	0.0
Other Extrapyramidal Event	2	2.7	2	2.7	4	2.7	0	0.0

Table 16 presents a listing of patients with adverse reactions associated with extrapyramidal symptoms in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration).

Table 16: Adverse Reactions Associated with Extrapyramidal Symptoms in a Placebo-Controlled Trial in Children and Adolescent Patients with Bipolar I Mania (3-week duration)

Preferred Term[1]	Quetiapine 400 mg/day (N=95)		Quetiapine 600 mg/day (N=98)		All Quetiapine (N=193)		Placebo (N=90)	
	n	%	n	%	n	%	n	%
Parkinsonism	2	2.1	1	1.0	3	1.6	1	1.1
Akathisia	1	1.0	1	1.0	2	1.0	0	0.0
Other Extrapyramidal Event	1	1.1	1	1.0	2	1.0	0	0.0

1. There were no adverse reactions with the preferred term of dystonic or dyskinetic events.

Laboratory, ECG, and vital sign changes observed in clinical studies
Laboratory Changes:
Neutrophil Counts
Adults: In placebo-controlled monotherapy clinical trials involving 3368 patients on quetiapine and 1515 on placebo, the incidence of at least one occurrence of neutrophil count $< 1.0 \times 10^9$/L among patients with a normal baseline neutrophil count and at least one available follow up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine, compared to 0.1% (2/1349) in patients treated with placebo*(see Warnings and Precautions (5.10))*.
Transaminase Elevations
Adults: Asymptomatic, transient, and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials in adults, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% (29/483) for quetiapine compared to 1% (3/194) for placebo. In acute bipolar mania trials in adults, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both quetiapine (3/560) and placebo (3/294). These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with quetiapine. In bipolar depression trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% (5/698) for quetiapine and 2% (6/347) for placebo.
Decreased Hemoglobin
Adults: In short-term placebo-controlled trials, decreases in hemoglobin to ≤ 13 g/dL males, ≤ 12 g/dL females on at least one occasion occurred in 8.3% (594/7155) of quetiapine-treated patients compared to 6.2% (219/3536) of patients treated with placebo. In a database of controlled and uncontrolled clinical trials, decreases in hemoglobin to ≤ 13 g/dL males, ≤ 12 g/dL females on at least one occasion occurred in 11% (2277/20729) of quetiapine-treated patients.
Interference with Urine Drug Screens
There have been literature reports suggesting false positive results in urine enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Caution should be exercised in the interpretation of positive urine drug screen results for these drugs, and confirmation by alternative analytical technique (e.g., chromatographic methods) should be considered.
ECG Changes
Adults: Between-group comparisons for pooled placebo-controlled trials revealed no statistically significant quetiapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for quetiapine compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for quetiapine compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for quetiapine compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to > 120 beats per minute. Quetiapine use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia in adults may be related to quetiapine potential for inducing orthostatic changes *(see Warnings and Precautions (5.7))*.
Children and Adolescents: In the acute (6-week) schizophrenia trial in adolescents, increases in heart rate (> 110 bpm) occurred in 5.2% (3/73) of patients receiving quetiapine 400 mg and 8.5% (5/74) of patients receiving quetiapine 800 mg compared to 0% (0/75) of patients receiving placebo. Mean increases in heart rate were 3.8 bpm and 11.2 bpm for quetiapine 400 mg and 800 mg groups, respectively, compared to a decrease of 3.3 bpm in the placebo group *(see Warnings and Precautions (5.7))*.
In the acute (3-week) bipolar mania trial in children and adolescents, increases in heart rate (> 110 bpm) occurred in 1.1% (1/89) of patients receiving quetiapine 400 mg and 4.7% (4/85) of patients receiving quetiapine 600 mg compared to 0% (0/98) of patients receiving placebo. Mean increases in heart rate were 12.8 bpm and 13.4 bpm for quetiapine 400 mg and 600 mg groups, respectively, compared to a decrease of 1.7 bpm in the placebo group *(see Warnings and Precautions (5.7))*.
In an acute (8-week) quetiapine extended-release tablets trial in children and adolescents (10 to 17 years of age) with bipolar depression, in which efficacy was not established, increases in heart rate (> 110 bpm 10 to 12 years and 13 to 17 years) occurred in 0% of patients receiving quetiapine extended-release tablets and 1.2% of patients receiving placebo. Mean increases in heart rate were 3.4 bpm for quetiapine extended-release tablets, compared to 0.3 bpm in the placebo group *(see Warnings and Precautions (5.7))*.

6.2 Postmarketing Experience
The following adverse reactions were identified during post approval of quetiapine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.
Adverse reactions reported since market introduction which were temporally related to quetiapine therapy include anaphylactic reaction, cardiomyopathy, drug reaction with eosinophilia and systemic symptoms (DRESS), hyponatremia, myocarditis, nocturnal enuresis, pancreatitis, retrograde amnesia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), decreased platelet count, serious liver reactions (including hepatitis, liver necrosis, and hepatic failure), agranulocytosis, intestinal obstruction, ileus, colon ischemia, urinary retention, sleep apnea, acute generalized exanthematous pustulosis (AGEP) , confusional state and cutaneous vasculitis.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Quetiapine
The risks of using quetiapine in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of quetiapine, caution should be used when it is taken in combination with other centrally acting drugs. Quetiapine potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be limited while taking quetiapine.
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.
CYP3A4 inhibitors:
Coadministration of ketoconazole, a potent inhibitor of cytochrome CYP3A4, resulted in significant increase in quetiapine exposure. The dose of quetiapine should be reduced to one sixth of the original dose if co-administered with a strong CYP3A4 inhibitor *(see Dosage and Administration (2.5) and Clinical Pharmacology (12.3))*.
CYP3A4 inducers:
Coadministration of quetiapine and phenytoin, a CYP3A4 inducer increased the mean oral clearance of quetiapine by 5 fold. Increased doses of quetiapine up to 5 fold may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other known potent CYP3A4 inducers *(see Dosage and Administration (2.6) and Clinical Pharmacology (12.3))*. When the CYP3A4 inducer is discontinued, the dose of quetiapine should be reduced to the original level within 7 to 14 days *(see Dosage and Administration (2.6))*.
Anticholinergic Drugs:
Concomitant treatment with quetiapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility. Quetiapine should be used with caution in patients receiving medications having anticholinergic (antimuscarinic) effects *(see Warnings and Precautions (5.20))*.
The potential effects of several concomitant medications on quetiapine pharmacokinetics were studied *(see Clinical Pharmacology (12.3))*.

7.2 Effect of Quetiapine on Other Drugs
Because of its potential for inducing hypotension, quetiapine may enhance the effects of certain antihypertensive agents.
Quetiapine may antagonize the effects of levodopa and dopamine agonists.
There are no clinically relevant pharmacokinetic interactions of quetiapine on other drugs based on the CYP pathway. Quetiapine and its metabolites are non-inhibitors of major metabolizing CYP's (1A2, 2C9, 2C19, 2D6, and 3A4).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Pregnancy Exposure Registry
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including quetiapine, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/
Risk Summary
Neonates exposed to antipsychotic drugs (including quetiapine) during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall available data from published epidemiologic studies of pregnant women exposed to quetiapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia, bipolar I, or major depressive disorder, and with exposure to antipsychotics, including quetiapine, during pregnancy *(see Clinical Considerations)*.
In animal studies, embryo-fetal toxicity occurred including delays in skeletal ossification at approximately 1 and 2 times the maximum recommended human dose (MRHD) of 800 mg/day in both rats and rabbits, and an increased incidence of carpal/tarsal flexure (minor soft tissue anomaly) in rabbit fetuses at approximately 2 times the MRHD. In addition, fetal weights were decreased in both species. Maternal toxicity (observed as decreased body weights and/or death) occurred at 2 times the MRHD in rats and approximately 1 to 2 times the MRHD in rabbits.
The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.
Clinical Considerations
Disease-associated maternal and/or fetal risk
There is a risk to the mother from untreated schizophrenia, or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.
A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.
Fetal/neonatal adverse reactions
Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including quetiapine, during the third trimester of pregnancy. These symptoms varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.
Data
Human Data
Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk of major birth defects.
Animal Data
When pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was no teratogenic effect in fetuses. Doses were 25, 50 and 200 mg/kg in rats and 25, 50 and 100 mg/kg in rabbits which are approximately 0.3, 0.6 and 2-times (rats) and 0.6, 1 and 2-times (rabbits) the MRHD for schizophrenia of 800 mg/day based on mg/m^2 body surface area. However, there was evidence of embryo-fetal toxicity including delays in skeletal ossification at approximately 1 and 2 times the MRHD of 800 mg/day in both rats and rabbits, and an increased incidence of carpal/tarsal flexure (minor soft tissue anomaly) in rabbit fetuses at approximately 2 times the MRHD. In addition, fetal weights were decreased in both species. Maternal toxicity (observed as decreased body weights and/or death) occurred at 2 times the MRHD in rats and approximately 1 to 2 times the MRHD (all doses tested) in rabbits.
In a peri/postnatal reproductive study in rats, no drug-related effects were observed when pregnant dams were treated with quetiapine at doses 0.01, 0.1, and 0.2 times the MRHD of 800 mg/day based on mg/m^2 body surface area. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 3 times the MRHD.

8.2 Lactation
Risk Summary
Limited data from published literature report the presence of quetiapine in human breast milk at relative infant dose of $< 1\%$ of the maternal weight-adjusted dosage. There are no consistent adverse events that have been reported in infants exposed to quetiapine through breast milk. There is no information on the effects of quetiapine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for quetiapine and any potential adverse effects on the breastfed child from quetiapine or from the mother's underlying condition.

8.3 Females and Males of Reproductive Potential
Infertility
Females
Based on the pharmacologic action of quetiapine (D2 antagonism), treatment with quetiapine may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *(see Warnings and Precautions (5.15))*.

8.4 Pediatric Use
In general, the adverse reactions observed in children and adolescents during the clinical trials were similar to those in the adult population with few exceptions. Increases in systolic and diastolic blood pressure occurred in children and adolescents and did not occur in adults. Orthostatic hypotension occurred more frequently in adults (4 to 7%) compared to children and adolescents ($< 1\%$) *(see Warnings and Precautions (5.7) and Adverse Reactions (6.1))*.
Schizophrenia
The efficacy and safety of quetiapine in the treatment of schizophrenia in adolescents aged 13 to 17 years were demonstrated in one 6-week, double-blind, placebo-controlled trial *(see Indications and Usage (1.1), Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Studies (14.1))*.
Safety and effectiveness of quetiapine in pediatric patients less than 13 years of age with schizophrenia have not been established.
Maintenance
The safety and effectiveness of quetiapine in the maintenance treatment of bipolar disorder has not been established in pediatric patients less than 18 years of age. The safety and effectiveness of quetiapine in the maintenance treatment of schizophrenia has not been established in any patient population, including pediatric patients.
Bipolar Mania
The efficacy and safety of quetiapine in the treatment of mania in children and adolescents ages 10 to 17 years with bipolar I disorder was demonstrated in a 3-week, double-blind, placebo-controlled, multicenter trial *(see Indications and Usage (1.2), Dosage and Administration (2.3), Adverse Reactions (6.1), and Clinical Studies (14.2))*.
Safety and effectiveness of quetiapine in pediatric patients less than 10 years of age with bipolar mania have not been established.
Bipolar Depression
Safety and effectiveness of quetiapine in pediatric patients less than 18 years of age with bipolar depression have not been established. A clinical trial with quetiapine extended-release tablets was conducted in children and adolescents (10 to 17 years of age) with bipolar depression, efficacy was not established.
Some differences in the pharmacokinetics of quetiapine were noted between children/adolescents (10 to 17 years of age) and adults. When adjusted for weight, the AUC and C_{max} of quetiapine were 41% and 39% lower, respectively, in children and adolescents compared to adults. The pharmacokinetics of the active metabolite, norquetiapine, were similar between children/adolescents and adults after adjusting for weight *(see Clinical Pharmacology (12.3))*.

8.5 Geriatric Use
Of the approximately 3700 patients in clinical studies with quetiapine, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of quetiapine in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to quetiapine, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients *(see Clinical Pharmacology (12.3) and Dosage and Administration (2.3))*.

8.6 Renal Impairment
Clinical experience with quetiapine in patients with renal impairment is limited *(see Clinical Pharmacology (12.3))*.

8.7 Hepatic Impairment
Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in patients with hepatic impairment. In this population, a low starting dose of 25 mg/day is recommended and the dose may be increased in increments of 25 mg/day to 50 mg/day *(see Dosage and Administration (2.4) and Clinical Pharmacology (12.3))*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
Quetiapine are not a controlled substance.

9.2 Abuse
Quetiapine have not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of quetiapine, e.g., development of tolerance, increases in dose, drug-seeking behavior.

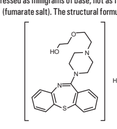
10 OVERDOSAGE

10.1 Human Experience
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. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness, sedation, tachycardia, hypotension, and anticholinergic toxicity including coma and delirium. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose *(see Warnings and Precautions (5.12))*. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first-degree heart block. In post-marketing experience, there were cases reported of QT prolongation with overdose.

10.2 Management of Overdosage
Establish and maintain an airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.
Appropriate supportive measures are the mainstay of management. For the most up-to-date information on the management of quetiapine overdosage, contact a certified Regional Poison Control Center (1-800-222-1222).

11 DESCRIPTION

Quetiapine is an atypical antipsychotic belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-Dibenzo [*b,f*] [1,4]thiazepin-11-yl-1-piperazinyl)-ethoxy] ethanol fumarate (2:1) (salt). 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 $(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.1 (fumarate salt). The structural formula is:



Quetiapine fumarate USP is a white to off-white crystalline powder which is sparingly soluble in 0.1N hydrochloric acid, slightly soluble in water, in anhydrous ethanol and in methanol.
Quetiapine tablets USP are supplied for oral administration as 25 mg (round, peach), 50 mg (round, white), 100 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.
Inactive ingredients are dibasic calcium phosphate dihydrate, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate and titanium dioxide.
The 25 mg tablets contain red iron oxide and yellow iron oxide and the 100 mg and 400 mg tablets contain only yellow iron oxide.
Each 25 mg tablet contains 28.78 mg of quetiapine fumarate USP equivalent to 25 mg quetiapine. Each 50 mg tablet contains 57.56 mg of quetiapine fumarate USP equivalent to 50 mg quetiapine. Each 100 mg tablet contains 115.13 mg of quetiapine fumarate USP equivalent to 100 mg quetiapine. Each 200 mg tablet contains 230.24 mg of quetiapine fumarate USP equivalent to 200 mg quetiapine. Each 300 mg tablet contains 345.36 mg of quetiapine fumarate USP equivalent to 300 mg quetiapine. Each 400 mg tablet contains 460.48 mg of quetiapine fumarate USP equivalent to 400 mg quetiapine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
The mechanism of action of quetiapine in the listed indications is unclear. However, the efficacy of quetiapine in these indications could be mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. The active metabolite, N-desalkyl quetiapine (norquetiapine), has similar activity at D_2, but greater activity at $5HT_{1A}$ receptors, than the parent drug (quetiapine).

12.2 Pharmacodynamics
Quetiapine and its metabolite, norquetiapine, have affinity for multiple neurotransmitter receptors with norquetiapine binding with higher affinity than quetiapine in general. The K values for quetiapine and norquetiapine at the dopamine D_1 are 428/99.8 nM, at D_2 626/489nM, at serotonin $5HT_{1A}$ 1040/191 nM at $5HT_{2A}$ 38/2.9 nM, at histamine H$_1$ 4.4/1.1 nM, at muscarinic M, 1086/38.3 nM, and at adrenergic α_1 b 14.8/46.4 nM and, at α_2 receptors 617/1290 nM, respectively.. Quetiapine and norquetiapine lack appreciable affinity to the benzodiazepine receptors.
Effect on QT Interval
In clinical trials, quetiapine was not associated with a persistent increase in QT intervals. However, the QT effect was not systematically evaluated in a thorough QT study. In post marketing experience, there were cases reported of QT prolongation in patients who overdosed on quetiapine *(see Overdosage (10.1))*, in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval.

12.3 Pharmacokinetics
Adults
Quetiapine 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.
Children and Adolescents
At steady state the pharmacokinetics of the parent compound, in children and adolescents (10 to 17 years of age), were similar to adults. However, when adjusted for dose and weight, AUC and C_{max} of the parent compound were 41% and 39% lower, respectively, in children and adolescents than in adults. For the active metabolite, norquetiapine, AUC and C_{max} were 45% and 31% higher, respectively, in children and adolescents than in adults. When adjusted for dose and weight, the pharmacokinetics of the metabolite, norquetiapine, was similar between children and adolescents and adults *(see Use in Specific Populations (8.4))*.
Absorption
Quetiapine 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 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
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.
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.
Age
Oral clearance of quetiapine was reduced by 40% in elderly patients ($\geq$ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary *(see Dosage and Administration (2.3))*.
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 to 30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr $>$ 80 mL/min/1.73 m^2, 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 *(see Use in Specific Populations (8.6))*.
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 C_{max} 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 *(see Dosage and Administration (2.4) and Use in Specific Populations (8.7))*.
Drug-Drug Interaction Studies
The *in vivo* assessments of effect of other drugs on the pharmacokinetics of quetiapine are summarized in Table 17 *(see Dosage and Administration (2.5 and 2.6) and Drug Interactions (7.1))*.

Table 17: The Effect of Other Drugs on the Pharmacokinetics of Quetiapine

Coadministered Drug	Dose Schedules		Effect on Quetiapine Pharmacokinetics
	Coadministered Drug	Quetiapine	
Phenytoin	100 mg three times daily	250 mg three times daily	5-fold increase in oral clearance
Divalproex	500 mg twice daily	150 mg twice daily	17% increase mean max plasma concentration at steady state. No effect on absorption or mean oral clearance
Thioridazine	200 mg twice daily	300 mg twice daily	65% increase in oral clearance
Cimetidine	400 mg three times daily for 4 days	150 mg three times daily	20% decrease in mean oral clearance
Ketoconazole (potent CYP 3A4 inhibitor)	200 mg once daily for 4 days	25 mg single dose	84% decrease in oral clearance resulting in a 6.2 fold increase in AUC of quetiapine
Fluoxetine	60 mg once daily	300 mg twice daily	No change in steady state PK
Imipramine	75 mg twice daily	300 mg twice daily	No change in steady state PK
Haloperidol	7.5 mg twice daily	300 mg twice daily	No change in steady state PK
Risperidone	3 mg twice daily	300 mg twice daily	No change in steady state PK

In vitro enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes CYP 1A2, 2C9, 2C19, 2D6, and 3A4. Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (Table 18) *(see Drug Interactions (7.2))*.

Table 18: The Effect of Quetiapine on the Pharmacokinetics of Other Drugs

Coadministered drug	Dose schedules		Effect on other drugs pharmacokinetics
	Coadministered drug	Quetiapine	
Lorazepam	2 mg, single dose	250 mg three times daily	Oral clearance of lorazepam reduced by 20%
Divalproex	500 mg twice daily	150 mg twice daily	C_{max} and AUC of free valproic acid at steady-state was decreased by 10-12%
Lithium	Up to 2400 mg/day given in twice daily doses	250 mg three times daily	No effect on steady-state pharmacokinetics of lithium
Antipyrine	1 g, single dose	250 mg three times daily	No effect on clearance of antipyrine or urinary recovery of its metabolites

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the MRHD of 800 mg/day based on mg/m^2 body surface area (mice) or 0.3, 1, and 3 times the MRHD based on mg/m^2 body surface area (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses 1.5 and 4.5 times the MRHD based on mg/m^2 body surface area and in male rats at a dose of 3 times the MRHD on mg/m^2 body surface area. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (0.3, 1, and 3 times the MRHD based on mg/m^2 body surface area).
Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.
Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-year toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown *(see Warnings and Precautions (5.15))*.
Mutagenesis
Quetiapine was not mutagenic or clastogenic in standard genotoxicity tests. The mutagenic potential of quetiapine was tested in the *in vitro* Ames bacterial gene mutation assay and in the *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. The clastogenic potential of quetiapine was tested in the *in vitro* chromosomal aberration assay in cultured human lymphocytes and in the *in vivo* bone marrow micronucleus assay in rats up to 500 mg/kg, which is 6 times the MRHD based on mg/m^2 body surface area.
Impairment of Fertility
Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or approximately 1 and 3 times the MRHD of 800 mg/day based on mg/m^2 body surface area. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 3 times the MRHD even after a two week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the MRHD based on mg/m^2 body surface area. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose approximately 1 times the MRHD of 800 mg/day based on mg/m^2 body surface area. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or approximately 0.1 and 1 times the MRHD of 800 mg/day based on mg/m^2 body surface area. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the MRHD of 800 mg/day based on mg/m^2 body surface area.

13.2 Animal Toxicology and/or Pharmacology
Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2-year carcinogenicity study. Doses were 10, 25, 50, 75, 150 and 250 mg/kg in rat studies which are approximately 0.1, 0.3, 0.6, 1, 2 and 3-times the MRHD of 800 mg/day based on mg/m^2 body surface area, respectively. Doses in the mouse carcinogenicity study were 20, 75, 250 and 750 mg/kg which are approximately