**HIGHLIGHTS OF PRESCRIBING INFORMATION**
**These highlights do not include all the information needed to use quetiapine fumarate tablets safely and effectively. See full prescribing information for quetiapine fumarate tablets .**

**Quetiapine Fumarate 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 is 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 antidepressant medications. (5.2)**
  - **Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.2)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Cerebrovascular Adverse Reactions, including Stroke in Elderly Patients with Dementia-Related Psychosis (5.3) 4/2014

----------INDICATIONS AND USAGE----------
Quetiapine is 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----------
- Quetiapine fumarate tablets can be taken with or without food (2.1)

| Indication | Initial Dose | Recommended Dose | Maximum Dose |
|---|---|---|---|
| Schizophrenia-Adults (2.2) | 25 mg twice daily | 150 to 750 mg/day | 750 mg/day |
| Schizophrenia-Adolescents (13 to 17 years) (2.2) | 25 mg twice daily | 400 to 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 to 800 mg/day | 800 mg/day |
| Bipolar Mania-Children and Adolescents (10 to 17 years), Monotherapy (2.5) | 25 mg twice daily | 400 to 600 mg/day | 600 mg/day |
| Bipolar Depression-Adults (2.2) | 50 mg once 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, 5.5)
- 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, 150 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 events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychosis 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 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 (5.8)
  - *Increased Blood Pressure in Children and Adolescents*: Monitor blood pressure at the beginning of, and periodically during treatment in children and adolescents (5.9)
  - *Leukopenia, Neutropenia and Agranulocytosis*: Monitor complete blood count frequently during the first few months of therapy in patients with a pre-existing low white cell count or a history of leukopenia/neutropenia. Consider discontinuation at the first sign of a decline in WBC in absence of other causative factors (5.9)
  - *Cataracts*: Lens changes have been observed in patients during long-term quetiapine treatment. Lens examination is recommended at initiation of treatment and at 6-month intervals during chronic treatment (5.10)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and twice placebo):
Adults: somnolence, dry mouth, dizziness, constipation, asthenia, abdominal pain, postural hypotension, dyspepsia, 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 Dr. Reddy's Laboratories Inc., at 1-888-375-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

----------DRUG INTERACTIONS----------
- Concomitant use of strong CYP3A4 inhibitors: Reduce quetiapine dose by one sixth when coadministered with strong CYP3A4 inhibitors (e.g., ketoconazole) (2.5, 7.1, 12.3)
- Concomitant use of strong CYP3A4 inducers: Increase quetiapine dose 5 fold when used in combination with a chronic treatment (more than 7 to 14 days) of potent CYP3A4 inducers (e.g., phenytoin, carbamazepine, St. John's Wort) (2.5, 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: Limited human data. Based on animal data, may cause fetal harm. Quetiapine should be used only if the potential benefit justifies the potential risk to fetus (8.1)
- Nursing Mothers: Discontinue drug or nursing, taking into consideration importance of drug to mother's health (8.3)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: December 2013**

**FULL PRESCRIBING INFORMATION: CONTENTS* RECENT MAJOR CHANGES**
**WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS**


**1 INDICATIONS AND USAGE**
1.1 Schizophrenia
1.2 Bipolar Disorder
1.3 Special Considerations in Treating Pediatric Schizophrenia and Bipolar I Disorder
**2 DOSAGE AND ADMINISTRATION**
2.1 Important Administration Instructions
2.2 Recommended Dosing
2.3 Dose Modifications in Elderly Patients
2.4 Dose Modifications in Hepatically Impaired Patients
2.5 Dose Modifications in Patients taking Weak or Moderate Inhibitors of Cytochrome P450 3A4 Activity
2.6 Dose Modifications when used with CYP3A4 Inhibitors
2.7 Dose Modifications when used with CYP3A4 Inducers
2.8 Reinitiation of Treatment in Patients Previously Discontinued
2.9 Switching from Antipsychotics
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
**5 WARNINGS AND PRECAUTIONS**
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults
5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
5.4 Neuroleptic Malignant Syndrome (NMS)
5.5 Metabolic Changes
5.6 Tardive Dyskinesia
5.7 Hypotension
5.8 Increases in Blood Pressure (Children and Adolescents)
5.9 Leukopenia, Neutropenia and Agranulocytosis
5.10 Cataracts
5.11 QT Prolongation
5.12 Seizures
5.13 Hypothyroidism
5.14 Hyperprolactinemia
5.15 Potential for Cognitive and Motor Impairment
5.16 Body Temperature Regulation
5.17 Dysphagia
5.18 Discontinuation Syndrome
**6 ADVERSE REACTIONS**
6.1 Clinical Study Experience
6.2 Post Marketing Experience
**7 DRUG INTERACTIONS**
7.1 Effect of Other Drugs on Quetiapine
7.2 Effect of Quetiapine on Other Drugs
**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
**9 DRUG ABUSE AND DEPENDENCE**
9.1 Controlled Substance
9.2 Abuse
**10 OVERDOSAGE**
10.1 Human Experience
10.2 Management of Overdosage
**11 DESCRIPTION**
**12 CLINICAL PHARMACOLOGY**
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
**14 CLINICAL STUDIES**
14.1 Schizophrenia
14.2 Bipolar Disorder
**16 HOW SUPPLIED/STORAGE AND HANDLING**
**17 PATIENT COUNSELING INFORMATION**


* Sections or subsections omitted from the full prescribing information are not listed.

**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 is 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 is 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 fumarate tablets are indicated for the treatment of schizophrenia. The efficacy of quetiapine fumarate 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 fumarate 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 fumarate 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 fumarate 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 fumarate 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 fumarate 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 and bipolar I disorder are serious mental disorders, however, diagnosis can be challenging. For pediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, manic episodes 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 of the risks and benefits of treatment with pharmacotherapy. Treatment for both pediatric schizophrenia and bipolar I disorder is indicated as part of a total treatment program that often includes counseling, psychosocial support, and other interventions.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 Important Administration Instructions

Quetiapine fumarate tablets can be taken with or without food.

### 2.2 Recommended Dosing

We recommend initial dose, titration, dose range and maximum quetiapine fumarate 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)**).

**Table 1:** Recommended Dosing for Quetiapine Fumarate Tablets

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

* N/A Not applicable

**Maintenance Treatment for Schizophrenia and Bipolar I Disorder**
**Maintenance Treatment**—Patients could 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 lower 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 **Warnings and Precautions (5.8)**). When clinically indicated, dose escalation should be performed with caution in these patients.

Elderly patients should be started on quetiapine fumarate 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 until an effective dose, depending on the clinical response and tolerability of the patient.

### 2.5 Dose Modifications when used with CYP3A4 Inhibitors

Quetiapine fumarate 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 fumarate tablets should be increased by 5 fold (see **Clinical Pharmacokinetics (12.3) and Drug Interactions (7.1)**).

### 2.6 Dose Modifications when used with CYP3A4 Inducers

Quetiapine fumarate tablets dose should be increased 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 fumarate 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 Reinitiation of Treatment in Patients Previously Discontinued

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

### 2.8 Switching from Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to quetiapine fumarate tablets, or concerning concomitant administration with other 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 from a depot antipsychotic, if medically appropriate, initiate quetiapine fumarate 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 fumarate tablets 25 mg are white, round, biconvex, film coated tablets debossed with 'R' on one side and '1' on other side
Quetiapine fumarate tablets 50 mg are white colored, round, biconvex, film coated tablets, debossed with 'R' on one side and '2' on other side
Quetiapine fumarate tablets 100 mg are off-white colored, round, biconvex, film coated tablets debossed with 'R' on one side and '3' on other side
Quetiapine fumarate tablets 150 mg are yellow colored, round, biconvex, film coated tablets debossed with 'RDY' on one side and '188' on other side
Quetiapine fumarate tablets 200 mg are white, round, biconvex, film coated tablets debossed with 'R' on one side and '5' on other side
Quetiapine fumarate tablets 300 mg are white colored, modified capsule shaped, biconvex, film coated tablets, debossed with 'R' on one side and '6' on other side
Quetiapine fumarate tablets 400 mg are yellow colored, capsule shaped, biconvex, film coated tablets, debossed with 'R' on one side and '7' on other side

## 4 CONTRAINDICATIONS

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

## 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 underlying psychosis or 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 drugs in over 4,400 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 there was 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<br>Increases Compared to Placebo |
|---|---|
| <18 | 14 additional cases |
| 18 to 24 | 5 additional cases |
| | **Decreases Compared to Placebo** |
| 25 to 64 | 1 fewer case |
| ≥65 | 6 fewer cases |

No suicides occurred in any of the pediatric trials. There were two suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect or 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 nonpsychiatric. 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 nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, the symptoms listed 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 overdosing.**

**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 in patients presenting with major depressive episode, patients 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 atypical antipsychotic drugs, and chronic, 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 fumarate. 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 creatine 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. 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. Quetiapine is not approved for treatment of schizophrenia or other psychotic disorders in NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinitiation 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 these metabolic disorders was observed. Patients with schizophrenia exhibit various 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 for patients being prescribed atypical antipsychotics and the lack of extensive data from controlled studies. 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 treatment-emergent 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.

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

| Laboratory Analyte | Category Change (All Least Once) from Baseline | Treatment Arm | N | Patients n (%) |
|---|---|---|---|---|
| Fasting Glucose | Normal to Impaired (≥100 mg/dL to ≥126 mg/dL) | Quetiapine | 2907 | 71 (2.4%) |
| | | Placebo | 1346 | 19 (1.4%) |
| | Impaired to Diabetic (≥126 mg/dL to ≥126 mg/dL) | Quetiapine | 572 | 27 (11.7%) |
| | | Placebo | 279 | 33 (11.8%) |

* Includes quetiapine and quetiapine extended release data.

In a 24-week (extra-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 treatment-emergent blood glucose level ≥ 200 mg/dL was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥ 126 mg/dL was 2.6%. The mean change in fasting glucose from baseline was 1.9 mg/dL and mean change in 2-hour glucose was 8.4 mg/dL for quetiapine treated patients.

In 2 long-term placebo-controlled randomized withdrawal clinical trials for bipolar I disorder maintenance, mean exposure of 213 days for quetiapine (640 patients) and 152 days for placebo (485 patients), the mean change in fasting glucose from baseline to endpoint was increased ~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 last meal, however, was higher for quetiapine treated patients (0.9 events per patient-year) versus patients treated with placebo (0.6 events per patient-year) for quetiapine (10.7% of patients; n=356) and 9.5 for placebo per 100 patient years (4.6% of patients; n=581).

### 5.6 Tardive Dyskinesia

In a 3-year uncontrolled maintenance monotherapy study in 222 patients (131 years of age) with schizophrenia (6 weeks duration), the mean change in fasting glucose levels for quetiapine (n=138) compared to placebo (n=47) was −0.75 mg/dL versus −1.70 mg/dL. In a placebo-controlled maintenance monotherapy study in adolescent patients with schizophrenia (6 weeks duration) treated with quetiapine (n=94) versus placebo (n=94), 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) at a baseline borderline fasting glucose level (≥100 mg/dL and <126 mg/dL) had a treatment-emergent blood glucose level of ≥126 mg/dL.

In a placebo-controlled maintenance monotherapy study in adult patients with bipolar disorder (duration of episodes not required) of age with bipolar depression, in which efficacy was not established, the mean change in fasting glucose levels for quetiapine extended release (n= 40) compared to placebo (n = 82) was 1.4 mg/dL versus −1.8 mg/dL. In this study, there were no patients in the quetiapine extended release 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 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

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 by Clinically Significant Levels by Indication**

| Laboratory Analyte | Indication | Treatment Arm | N | Patients n (%) |
|---|---|---|---|---|
| Total Cholesterol ≥240 mg/dL | Schizophrenia * | Quetiapine | 137 | 19 (18%) |
| | | Placebo | 92 | 6 (7%) |
| | Bipolar Depression * | Quetiapine | 463 | 41 (9%) |
| | | Placebo | 250 | 15 (6%) |
| Triglycerides ≥200 mg/dL | Schizophrenia * | Quetiapine | 120 | 26 (22%) |
| | | Placebo | 79 | 11 (16%) |
| | Bipolar Depression * | Quetiapine | 436 | 59 (14%) |
| | | Placebo | 232 | 20 (8%) |
| LDL-Cholesterol ≥160 mg/dL | Schizophrenia * | Quetiapine | nr/ | nr/ |
| | | Placebo | nr/ | nr/ |
| | Bipolar Depression * | Quetiapine | 465 | 29 (6%) |
| | | Placebo | 256 | 12 (5%) |
| HDL-Cholesterol <40 mg/dL | Schizophrenia * | Quetiapine | nr/ | nr/ |
| | | Placebo | nr/ | nr/ |
| | Bipolar Depression * | Quetiapine | 393 | 56 (14%) |
| | | Placebo | 214 | 29 (14%) |

n: 6 weeks duration
b: 8 weeks duration
nr: Numbers not presented in the quetiapine registration studies for schizophrenia. Lipid parameters also were not measured in the bipolar mania registration studies.

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 * | Quetiapine | 107 | 13 (12%) |
| | | Placebo | 56 | 1 (2%) |
| | Bipolar Mania * | Quetiapine | 159 | 15 (10%) |
| | | Placebo | 66 | 2 (3%) |
| Triglycerides ≥150 mg/dL | Schizophrenia * | Quetiapine | 103 | 17 (17%) |
| | | Placebo | 51 | 4 (8%) |
| | Bipolar Mania * | Quetiapine | 149 | 32 (22%) |
| | | Placebo | 62 | 8 (13%) |
| LDL-Cholesterol ≥ 130 mg/dL | Schizophrenia * | Quetiapine | 112 | 4 (4%) |
| | | Placebo | 60 | 1 (2%) |
| | Bipolar Mania * | Quetiapine | 169 | 13 (8%) |
| | | Placebo | 74 | 4 (5%) |
| HDL-Cholesterol <40 mg/dL | Schizophrenia * | Quetiapine | 104 | 16 (15%) |
| | | Placebo | 54 | 10 (19%) |
| | Bipolar Mania * | Quetiapine | 154 | 16 (10%) |
| | | Placebo | 61 | 4 (7%) |

a: 13 to 17 years, 6 weeks duration
b: 10 to 17 years, 3 weeks duration
In a placebo-controlled quetiapine extended release 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 vs. 4% (5/84) for placebo; triglycerides 28% (23/80) for quetiapine extended release vs. 9% (7/80) for placebo; LDL-cholesterol 2% (2/80) for quetiapine extended release vs. 4% (3/85) for placebo and HDL-cholesterol 20

**Table 16: Adverse Reactions Associated with Sertraline Compared to Placebo in a Placebo-controlled Trial of Adults and Pediatrics with Bipolar I Mania (3-week duration)**

| Preferred Term* | Quetiapine 400 mg/day (N=95) | | Quetiapine 600 mg/day (N=95) | | All Quetiapine (N=190) | | Placebo (N=95) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Parkinsonism | 1 | 1.1 | 1 | 1.1 | 2 | 1.1 | 0 | 0 |
| Akathisia | | | | | | | | |
| Other Extrapyramidal Event | 1 | 1.1 | 1 | 1.1 | 2 | 1.1 | 0 | 0 |

* There were no adverse experiences with the preferred term of dystonic or dyskinetic events.

Other Adverse Reactions Observed During the Pre-Marketing Evaluation of Quetiapine

Following is a list of COSTART terms that reflect treatment-emergent adverse reactions as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with quetiapine at doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for schizophrenia. All reported reactions are included except those already listed in the tables or elsewhere in labeling, those reactions for which a drug cause was remote, those reactions for which terms were too general as to be uninformative, it is important to emphasize that, although the reactions reported occurred during treatment with quetiapine, they were not necessarily caused by quetiapine.

Reactions are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those not already listed in the tabulated results that occurred in at least one patient (rare reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients).

Nervous System: **Infrequent:** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased, ataxia, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; **Rare:** aphasia, choreoathetosis, dysarthria, grand mal convulsion, hypertonia, libido decreased*, neuralgia, stabbing, suicidal hallucinations.

Body as a Whole: **Frequent:** flu syndrome; **Infrequent:** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdomen enlarged.

Digestive System: **Frequent:** anorexia; **Infrequent:** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, esophagitis, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: **Infrequent:** vasodilatation, ECG abnormal, congestive heart failure, angina pectoris, sinus arrhythmia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, Cheyne-Stokes respiration, myocardial infarction, pulmonary embolism, T wave flattening, ST depression, increased QRS duration.

Respiratory System: **Frequent:** cough increased; **Infrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccup, hypoventilation.

Metabolic and Nutritional System: **Infrequent:** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hypercalcemia, creatinine increased, hypercholesterolemia; **Rare:** glycosuria, gout, hard edema, hypokalemia, water intoxication.

Skin and Appendages System: **Infrequent:** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; **Rare:** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: **Infrequent:** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, menstrual disorder*, cystitis, urinary frequency, amenorrhea*, female lactation*, breast enlargement, polyuria, leukorrhea*, breast pain*, gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: **Infrequent:** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; **Rare:** amblyopia, abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: **Infrequent:** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: **Infrequent:** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia, lymphadenopathy, cyanosis; **Rare:** hemolysis, thrombocythemia.

Endocrine System: **Infrequent:** hypothyroidism, diabetes mellitus; **Rare:** hyperthyroidism.

* Adjusted for gender.

**Laboratory, ECG and vital sign changes observed in clinical studies**

Laboratory Changes:

Hematological Changes

Adults: In placebo-controlled monotherapy clinical trials involving 3368 patients on quetiapine fumarate and 1515 on placebo, the incidence of at least one occurrence of neutrophil count <1.0109/L observed in patients with a normal baseline neutrophil count at least one available follow-up laboratory measurement was 0.3% (10/2967) in patients treated with quetiapine fumarate, compared to 0.1% (2/1349) in patients treated with placebo. [see **Warnings and Precautions (5.9)**].

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% (294/5023) 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 treatment with quetiapine in these trials. In these trials 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% (5/498) for quetiapine and 2% (6/247) for placebo.

Decreased Hemoglobin

Adults: In seven placebo-controlled trials, decreases in hemoglobin to ≤ 13 g/dL males, ≤ 12 g/dL females in patients at least one occasion occurred in 8.3% (594/7135) 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% (227/2029) 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 been 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.

Vital Signs:

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 observed in four 3- to 6-week placebo-controlled trials in adult patients with a diagnosis of schizophrenia revealing a 1% (4/289) incidence for quetiapine compared to 0.8% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia were 5.5% (1/182) for quetiapine compared to 0% (0/79) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria were 0.8% (1/166) for quetiapine compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patient 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-treated patients. This slight tendency to tachycardia in adults may be related to quetiapine's potential for inducing orthostatic changes [**see Warnings and Precautions (5.7)**].

*Children and Adolescents:*

In the acute (6 week) schizophrenia trials in adolescents, increases in heart rate (> 110 bpm) occurred in 5.2% (3/73) of patients receiving quetiapine 400 mg and 8.8% (5/74) of patients receiving quetiapine 800 mg compared with 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 lithium and 0.0% (0/88) 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 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 placebo, in 1% of patients receiving extended release and 1.2% of patients receiving placebo. Mean increases in heart rate were 3.4 bpm for quetiapine extended release, compared to 0.3 bpm in the placebo group [**Warnings and Precautions (5.7)**].

**8.2 Post Marketing 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.

Cardiac disorders: sinus tachycardia; myocardial infarction which were temporally related to quetiapine therapy; include pulmonary/ischemic cardiomyopathy, hypokinesia, myocarditis, nocturnal enuresis, retrograde amnesia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

## 9 DRUG INTERACTIONS

**9.1 Effect of Other Drugs on Quetiapine**

The risk 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 stable patients with schizophrenia. Quetiapine should be used with caution while taking quetiapine.

Quetiapine exposure is increased by the prototype CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, imidazole, 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 coadministered 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 quetiapine is added to or discontinued, the dose of quetiapine should be reduced to the original level within 7 to 14 days [**see Dosage and Administration (2.6)**].

The potential effects of several concomitant medications on quetiapine pharmacokinetics were studied [**see Clinical Pharmacology (12.3)**].

**9.2 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 CYPs (1A2, 2D6, 2C9, 2C8, and 3A4).

## 10 USE IN SPECIFIC POPULATIONS

**10.1 Pregnancy**

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of quetiapine use in pregnant women. In limited published literature, there were no major malformations associated with quetiapine exposure during pregnancy in animal studies, embryo-fetal toxicity occurred. Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Data

There are limited published data on the use of quetiapine for treatment of schizophrenia and other psychiatric disorders during pregnancy. In a prospective observational study, 21 women exposed to quetiapine and other psychoactive medications during pregnancy were followed for major malformations. Among 42 other infants born to pregnant women who used quetiapine during pregnancy, there were no major malformations reported (rate of major birth defects 0% versus 2.4% in the general population). In these published reports, these patients reporting data did not reliably estimate the frequency or absence of adverse outcomes. Neonates exposed to antipsychotic drugs (including quetiapine), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. These have been reported as 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 hospitalization.

Animal Data

When pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was no teratogenic effect at doses up to 2.4 times the maximum recommended human dose (MRHD) for schizophrenia (based on mg/m² body surface area). However, quetiapine was found to be a teratogen of embryo-fetal toxicity, which included delays in skeletal ossification occurring at approximately 1 and 2 times the MRHD of 800 mg/day in both rats and rabbits, and an increased incidence of cryptorchidism in rats at a dose 2 times the MRHD, with no effect observed at 0.3 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, in the teratology studies.

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, 0.12, and 0.24 times the MRHD of 800 mg/day based on mg/m² body surface area. However, in a preliminary peri/postnatal study, there was an increase in fetal and pup death, and decreases in mean pup weight at 3 times the MRHD.

**10.2 Labor and Delivery**

The effect of quetiapine on labor and delivery in humans is unknown.

**10.3 Nursing Mothers**

Quetiapine was excreted into human milk. Because of the potential for serious adverse reactions in nursing infants from quetiapine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother's health.

In published case reports, the level of quetiapine in breast milk ranged from undetectable to 170 ng/mL.

An estimated infant dose ranged from 0.09% to 0.47% of a weight-adjusted maternal dose. Based on a limited number (N=8) of mother/infant pairs, calculated infant daily doses range from less than 0.01 mg/kg (at a maternal daily dose up to 100 mg quetiapine) to 0.1 mg/kg (at a maternal daily dose of 400 mg).

**10.4 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 established in a 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 aged 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 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 57% lower 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)**].

**10.5 Geriatric Use**

Of the approximately 3700 patients in clinical studies with quetiapine, 7% (222) 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 is not a controlled substance.

**9.2 Abuse**

Quetiapine has 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 signs of misuse and abuse, quetiapine should be prescribed or dispensed in limited quantities consistent with good clinical practice.

## 9 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 drugs 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 [**see Warnings and Precautions (5.7)**]. One case, involving an estimated overdose of 9600 mg, was associated with hyponatremia and first degree heart block. In post-marketing experience, there were cases reported of QT prolongation with overdose. There were also very rare reports of overdose of quetiapine alone resulting in coma or death.

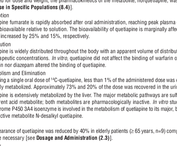
**10.2 Management of Overdosage**

In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT prolonging effects when administered in patients with acute overdosage of quetiapine. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to quetiapine. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

## 10 DESCRIPTION

Quetiapine fumarate is a psychotropic agent 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 $C_{42}H_{50}N_6O_4S_2$ and its molecular weight is $C_{42}H_{50}N_6O_4S_2$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder soluble in DMF, slightly soluble in methanol..

Quetiapine fumarate tablets are supplied for oral administration as 25 mg (round, white), 50 mg (round, white), 100 mg (round, yellow), 150 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.

Inactive ingredients are colloidal silicon dioxide, dibasic calcium phosphate dehydrate (fine powder), lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate.

The 25 mg, 50 mg, 200 mg and 300 mg tablets contain opaqry white OY58980 (hypromellose 5 cp, polyethylene glycol 400, titanium dioxide) and 100 mg, 150 mg and 400 mg tablets contains opaqry yellow OY32945 (hypromellose 5 cp, iron oxide yellow, polyethylene glycol 400, titanium dioxide).

## 12 CLINICAL PHARMACOLOGY

**12.1 Mechanism of Action**

The mechanism of action of quetiapine is unknown. However, it has been proposed that the efficacy of quetiapine in schizophrenia and its mood stabilizing properties in bipolar depression and mania are mediated through a combination of dopamine type 2 (D2) and serotonin type 2 (5HT2) antagonism. Antagonism at receptors other than dopamine and 5HT2 with similar receptor affinities may explain some of the other effects of quetiapine.

Quetiapine's antagonism of histamine $H_1$ receptors may explain the sedative effects observed with this drug.

Quetiapine's antagonism of adrenergic $\alpha_1$ receptors may explain the orthostatic hypotension observed with this drug.

**12.2 Pharmacodynamics**

Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: serotonin 5HT$_{1A}$ and 5HT$_{2}$ ($IC_{50}$=717 & 148nM, respectively), dopamine $D_1$ and $D_2$ ($IC_{50}$=1388 & 329nM, respectively), histamine $H_1$ ($IC_{50}$=30nM), and adrenergic $\alpha_1$ and $\alpha_2$ receptors ($IC_{50}$=94 & 271nM, respectively). Quetiapine has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors ($IC_{50}$>5000 nM).

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 fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed dosage 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, when adjusted for dose and weight. AUC and $C_{max}$ of the parent compound were 41% and 29% 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 (10.4)**].

Absorption

Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with $C_{max}$ 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 (≥ 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 (Ccr<10 to 30 mL/min/1.73 m², n=8) had a 25% lower mean oral clearance than normal subjects (Ccr >80 mL/min/1.73 m², n=8), but patients with moderate renal insufficiency were within the range of corresponding normal subjects. Adverse reactions were 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 | 150 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 mgtwice daily | 65% increase in oral clearance |
| Cimetidine | 400 mg three times daily for 4days | 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, 2D6, 2C19, 2C9, and 3A4. Quetiapine at doses of 250 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 | Cmax and AUC of free valproic acid at steady-state was decreased by 10 to 15% |
| 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 | 1g, 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 20, 75, and 250 mg/kg for 2 years. These doses were approximately 0.1, 0.3, 1.5, and 4.5 times the maximum human dose (MRHD) of 800 mg/day based on mg/m² body surface area (mrsc) or 0.3, 1, and 3 times the MRHD based on mg/m² body surface area (crats). There were no treatment-emergent tumors in the mouse carcinogenicity study. In female rats, at dose of 20 and 75 times the MRHD on mg/m² body surface area and in male rats at a dose of 3 times the MRHD on mg/m² body surface area, Mammary gland adenocarcinoma were statistically significantly increased. In female rats at all doses (3,1, and 3 times the MRHD on mg/m² body surface area) Pituitary gland tumors were observed.

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 rodent 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 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 (5.14)**].

Mutagenesis

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. Doses up to 500 mg/kg which is approximately the maximum recommended human dose on mg/m² body surface area. Based on weight of evidence quetiapine was not mutagenic or clastogenic in these tests.

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 maximum human dose (MRHD) of 800 mg/day based on mg/m² body surface area. These effects included increased mating time, decreased fertility index 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 exposure to quetiapine. No effect on fertility was observed in female rats treated with quetiapine at doses up to 3 times the MRHD dose on mg/m² 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 on mg/m² body surface area. Drug-related effects included decreased implantation sites in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrous cycles was observed at doses of 10 and 50 mg/kg, or approximately 0.1 and 1 times the MRHD of 800 mg/day on mg/m² body surface area. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the MRHD of 800 mg/day on mg/m² 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 to 250 mg/kg in the rat and 75 to 750 mg/kg in mice; these doses are 0.1 to 3, and 0.1 to 4.5 times the maximum recommended human dose (MRHD) of 800 mg/day on mg/m² body surface area, respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but it was found to be chemically distinct from melanin or thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

Quetiapine administration for 2 weeks to dogs at doses of 20 to 100 mg/kg and for 13 weeks at doses of 20 mg/kg caused bilateral cataracts in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the MRHD of 800 mg/day on mg/m² body surface area. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine-caused lens cataracts were observed in dogs treated with a lower-dosage drug and monkeys studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of defined cholesterol crystals in the lens of dogs treated with quetiapine was not observed in monkeys. In dogs, there was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in dogs given quetiapine for up to a 1-year study in monkeys, in rodent studies, or in patients. Lens opacity of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the MRHD of 800 mg/day on mg/m² body surface area.

## 14 CLINICAL STUDIES

**14.1 Schizophrenia**

**Short-term Studies**

The efficacy of quetiapine in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM-IV criteria for schizophrenia. Schizophrenia was characterized by a variety of symptoms and it was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of quetiapine and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item rating scale of severity of psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior,