QUETIAPINE FUMARATE - quetiapine fumarate tablet, film coated
REMEDYREPACK INC.

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 Initial U.S. Approval: 1997

Boxed Warning section

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen 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 Warnings and Precautions (5.1)]*.

BOXED WARNING

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of quetiapine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. 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 in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Quetiapine is not approved for use in patients under ten years of age [*see Warnings and Precautions (5.2)]*.

INDICATIONS & USAGE

Quetiapine fumarate tablet is indicated for the treatment of schizophrenia. The efficacy of quetiapine fumarate tablets in schizophrenia was established in three 6- week trials in adults. 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*)].

Pediatric use information in patients (13 to 17 years of age) with schizophrenia is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those adolescent patients.

Quetiapine fumarate tablet is 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. [*see Clinical Studies* (*14.2*)].

Quetiapine fumarate tablet is 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*)].

Pediatric use information in patients (10 to 17 years of age) with bipolar mania is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those pediatric patients.

Pediatric use information in patients (13 to 17 years of age) with schizophrenia, and patients (10 to 17 years of age) with bipolar mania is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those patients.

DOSAGE & ADMINISTRATION

Quetiapine fumarate tablets can be taken with or without food.

Adults

Dose Selection— Quetiapine fumarate tablets should generally be administered with an initial dose of 25 mg twice daily, with increases in total daily dose of 25 mg to 50 mg divided in two or three doses on the second and third day, as tolerated, to a total dose range of 300 mg to 400 mg daily by the fourth day. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady-state for quetiapine fumarate tablets would not be achieved for approximately 1 to 2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25 mg to 50 mg divided twice daily are recommended. Most efficacy data with quetiapine fumarate tablets were obtained using three times daily dosing regimens, but in one controlled trial 225 mg given twice per day was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 mg/day to 750 mg/day in the clinical trials supporting the effectiveness of quetiapine fumarate tablets. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400 mg/day to 500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Maintenance Treatment— The effectiveness of quetiapine fumarate tablets for longer than 6 weeks has not been evaluated in controlled clinical trials. While there is no body of evidence available to answer the question of how long the patient treated with quetiapine fumarate tablets should be maintained, it is

generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Adolescents (13 to 17 years)

Pediatric dosing information in patients (13 to 17 years of age) with schizophrenia is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those adolescent patients.

Adults

Acute Treatment of Manic Episodes in Bipolar I Disorder

Dose Selection—When used as monotherapy or adjunct therapy (with lithium or divalproex), quetiapine fumarate tablets should be initiated in twice daily doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in twice daily divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicate that the majority of patients responded between 400 mg/day to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Acute Treatment of Depressive Episodes in Bipolar Disorder

Dose Selection— Quetiapine fumarate tablets should be administered once daily at bedtime to reach 300 mg/day by Day 4.

Recommended Dosing Schedule

Day	Day 1	Day 2	Day 3	Day 4
Quetiapine fumarate tablets	50 mg	100 mg	200 mg	300 mg

In the clinical trials supporting effectiveness, the dosing schedule was 50 mg, 100 mg, 200 mg and 300 mg/day for Days 1 to 4 respectively. Patients receiving 600 mg increased to 400 mg on Day 5 and 600 mg on Day 8 (Week 1). Antidepressant efficacy was demonstrated with quetiapine fumarate tablets at both 300 mg and 600 mg; however, no additional benefit was seen in the 600 mg group.

Maintenance Treatment of Bipolar I Disorder

Maintenance of efficacy in bipolar I disorder was demonstrated with quetiapine fumarate tablets (administered twice daily totaling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance phase, patients continued on the same dose on which they were stabilized during the stabilization phase [*see Clinical Studies* (*14.2*)].

Children and Adolescents (10 to 17 years)

Pediatric dosing information in patients (10 to 17 years of age) with bipolar mania is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those pediatric 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*)]. When indicated, dose escalation should be performed with caution in these 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.

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

There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to quetiapine fumarate 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 fumarate tablets therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be re-evaluated periodically.

DOSAGE FORMS & STRENGTHS

25 mg tablets

50 mg tablets

100 mg tablets

200 mg tablets

300 mg tablets

400 mg tablets

CONTRAINDICATIONS

None known

WARNINGS AND PRECAUTIONS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Quetiapine is not approved for the treatment of patients with dementia-related psychosis

(see Boxed Warning).

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 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	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 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 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, 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, 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. It should be noted that quetiapine is approved for use in treating adult bipolar depression.

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 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 (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.

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 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.

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 parameters should be managed as clinically appropriate.

Adults:

Table 2: Fasting Glucose—Proportion of Patients Shifting to ≥126 mg/dL in Short-Term (≤12 weeks) Placebo-Controlled Studies

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 ≥126 mg/dL)	Quetiapine	572	67 (11.7%)
		Placebo	279	33 (11.8%)

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 treatment-emergent post-glucose challenge 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 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 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 treatment-emergent blood glucose level of ≥126 mg/dL.

Undesirable alterations in lipids have been observed with quetiapine use. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using quetiapine is recommended.

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 parameters should be managed as clinically appropriate.

Adults:

Table 3 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 3: 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*	Quetiapine	137	24 (18%)
Placebo	92	6 (7%)		
Bipolar Depression†	Quetiapine	463	41 (9%)	
Placebo	250	15 (6%)		
Triglyceride ≥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‡	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%)		

Children and Adolescents: Table 4 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 4: 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	16 (10%)	
Placebo	66	2 (3%)		
Triglycerides ≥150 mg/dL	Schizophrenia[4]	Quetiapine	103	17 (17%)
Placebo	51	4 (8%)		
Bipolar Mania[5]	Quetiapine	149	32 (22%)	
Placebo	60	8 (13%)		
LDL-Cholesterol ≥ 130 mg/dL	Schizophrenia[4]	Quetiapine	112	4 (4%)
Placebo	60	1 (2%)		
Bipolar Mania[5]	Quetiapine	169	13 (8%)	
Placebo	74	4 (5%)		
HDL-Cholesterol ≤ 40 mg/dL	Schizophrenia[4]	Quetiapine	104	16 (15%)
Placebo	54	10 (19%)		
Bipolar Mania[5]	Quetiapine	154	16 (10%)	
Placebo	61	4 (7%)		

Increases in weight have been observed in clinical trials. Patients receiving quetiapine should receive regular monitoring of weight [see Patient Counseling Information (*17*)].

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 parameters should be managed as clinically appropriate.

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

Table 5: Proportion of Patients with Weight Gain ≥7% of Body Weight (Adults)

Vital Sign	Indication	Treatment Arm	N	Patients n (%)
Weight Gain ≥7% of Body Weight	Schizophrenia*	Quetiapine	391	89 (23%)
Placebo	206	11 (6%)		
Bipolar Mania (monotherapy)†	Quetiapine	209	44 (21%)	
Placebo	198	13 (7%)		
Bipolar Mania (adjunct therapy)‡	Quetiapine	196	25 (13%)	
Placebo	203	8 (4%)		
Bipolar Depression§	Quetiapine	554	47 (8%)	
Placebo	295	7 (2%)		

Children and Adolescents: In two clinical trials with quetiapine, one in bipolar mania and one in schizophrenia, reported increases in weight are included in the table below.

Table 6: Proportion of Patients with Weight Gain ≥7% of Body Weight (Children and Adolescents)

Vital Sign	Indication	Treatment Arm	N	Patients n (%)
Weight Gain ≥7% of Body Weight	Schizophrenia*	Quetiapine	111	23 (21%)
Placebo	44	3 (7%)		

Bipolar Mania†	Quetiapine	157	18 (12%)
	Placebo	68	0 (0%)

The mean change in body weight in the schizophrenia trial was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group and in the bipolar mania trial it was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group.

In an open-label study that enrolled patients from the above two pediatric trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

When treating pediatric patients with quetiapine for any indication, weight gain should be assessed against that expected for normal growth.

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs, including quetiapine. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, quetiapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on quetiapine, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (28/3265) of the patients treated with quetiapine, compared with 0.2% (2/954) on placebo and about 0.4% (2/527) on active control drugs. Orthostatic hypotension, dizziness, and syncope may lead to falls.

Quetiapine should be used with particular caution in patients with known cardiovascular disease (history

of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications) [*see Adverse Reactions* (*6.2*)]. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg twice daily [*see Dosage and Administration* (*2*)]. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

In placebo-controlled trials in children and adolescents with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of increases at any time in systolic blood pressure (≥20 mmHg) was 15.2% (51/335) for quetiapine and 5.5% (9/163) for placebo; the incidence of increases at any time in diastolic blood pressure (≥10 mmHg) was 40.6% (136/335) for quetiapine and 24.5% (40/163) for placebo. In the 26-week open-label clinical trial, one child with a reported history of hypertension experienced a hypertensive crisis. Blood pressure in children and adolescents should be measured at the beginning of, and periodically during treatment.

In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including quetiapine. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue quetiapine at the first sign of a decline in WBC in absence of other causative factors.

Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue quetiapine and have their WBC followed until recovery [*see Adverse Reactions* 6.2)].

The development of cataracts was observed in association with quetiapine treatment in chronic dog studies [*see Nonclinical Toxicology, Animal Toxicology* (*13.2*)]. Lens changes have also been observed in adults, children and adolescents during long-term quetiapine treatment, but a causal relationship to quetiapine use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment.

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 [*see Drug Interactions (7)*].

The use of quetiapine should be avoided in combination with other drugs that are known to prolong QTc including Class 1A antiarrythmics (e.g., quinidine, procainamide) or Class III antiarrythmics (e.g., amiodarone, sotalol), antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone).

Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsade

de pointes and/or sudden death including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

Caution should also be exercised when quetiapine is prescribed in patients with increased risk of QT prolongation (e.g. cardiovascular disease, family history of QT prolongation, the elderly, congestive heart failure and heart hypertrophy).

During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with quetiapine compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics, quetiapine should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Adults: Clinical trials with quetiapine demonstrated dose-related decreases in thyroid hormone levels. The reduction in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range was maximal in the first six weeks of treatment and maintained without adaptation or progression during more chronic therapy. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of quetiapine patients did experience TSH increases in monotherapy studies. Some patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where quetiapine was added to lithium or divalproex, 12% (24/196) of quetiapine treated patients compared to 7% (15/203) of placebo-treated patients had elevated TSH levels. Of the quetiapine treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels.

In all quetiapine trials, the incidence of potentially clinically significant shifts in thyroid hormones and TSH were*: decrease in free T4, 2.0% (357/17513); decrease in total T4, 4.0% (75/1861); decrease in free T3, 0.4% (53/13766); decrease in total T3, 2.0% (26/1312), and increase in TSH, 4.9% (956/19412). In eight patients, where TBG was measured, levels of TBG were unchanged.

Table 7 shows the incidence of these shifts in short-term placebo-controlled clinical trials.

Table 7: Incidence of potentially clinically significant shifts in thyroid hormone levels and TSH in short term placebo-controlled clinical trials*

Total T_4		Free T_4		Total T_3		Free T_3		TSH	
Quetiapine	Placebo	Quetiapine	Placebo	Quetiapine	Placebo	Quetiapine	Placebo	Quetiapine	Placebo
3.4 % (37/1097)	0.6% (4/651)	0.7% (52/7218)	0.1% (4/3668)	0.5% (2/369)	0.0% (0/113)	0.2% (11/5673)	0.0% (1/2679)	3.2% (240/7587)	2.7% (105/3912)

In short-term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0.0 % for both quetiapine (1/4800) and placebo (0/2190) and for T_4 and TSH the shifts were 0.1% (7/6154) for quetiapine versus 0.0% (1/3007) for placebo.

Generally, these changes in thyroid hormone levels were of no clinical significance.

Children and Adolescents: In acute placebo-controlled trials in children and adolescent patients with schizophrenia (6-week duration) or bipolar mania (3-week duration), the incidence of shifts to potentially clinically important thyroid function values at any time for quetiapine treated patients and placebo-treated patients for elevated TSH was 2.9% (8/280) vs. 0.7% (1/138), respectively and for decreased total thyroxine was 2.8% (8/289) vs. 0% (0/145, respectively). Of the quetiapine treated patients with elevated TSH levels, 1 had simultaneous low free T4 level at end of treatment.

Adults: During clinical trials with quetiapine, the incidence of shifts in prolactin levels to a clinically significant value occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo.

Children and Adolescents: In acute placebo-controlled trials in children and adolescent patients with bipolar mania (3-week duration) or schizophrenia (6-week duration), the incidence of shifts in prolactin levels to a clinically significant value (>20 µg/L males; > 26 µg/L females at any time) was 13.4% (18/134) for quetiapine compared to 4% (3/75) for placebo in males and 8.7% (9/104) for quetiapine compared to 0% (0/39) for placebo in females.

Like other drugs that antagonize dopamine D2 receptors, quetiapine elevates prolactin levels in some patients and the elevation may persist during chronic administration. Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in carcinogenicity studies conducted in mice and rats. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive [*see Carcinogenesis, Mutagenesis, Impairment of Fertility* (*13.1*)].

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.

Somnolence was a commonly reported adverse event reported in patients treated with quetiapine especially during the 3 to 5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% (89/510) of patients on quetiapine compared to 11% (22/206) of placebo patients. In acute bipolar mania trials using quetiapine as monotherapy, somnolence was reported in 16% (34/209) of patients on quetiapine compared to 4% of placebo patients. In acute bipolar mania trials using quetiapine as adjunct therapy, somnolence was reported in 34% (66/196) of patients on quetiapine compared to 9% (19/203) of placebo patients. In bipolar depression trials, somnolence was reported in 57% (398/698) of patients on quetiapine compared to 15% (51/347) of placebo patients. Since quetiapine has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that quetiapine therapy does not affect them adversely. Somnolence may lead to falls.

One case of priapism in a patient receiving quetiapine has been reported prior to market introduction. While a causal relationship to use of quetiapine has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that quetiapine may share this capacity. Severe priapism may require surgical intervention.

Although not reported with quetiapine, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing quetiapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Quetiapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. 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.

In two 8-week clinical studies in patients with bipolar depression (N=1048), the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo (quetiapine 300 mg, 6/350, 1.7%; quetiapine 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%).

Clinical experience with quetiapine in patients with certain concomitant systemic illnesses is limited [see *Pharmacokinetics* (*12.3*)].

Quetiapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with quetiapine, caution should be observed in cardiac patients see [*Warnings and Precautions* (*5.8*)].

Acute withdrawal symptoms, such as insomnia, nausea, and vomiting have been described after abrupt cessation of atypical antipsychotic drugs, including quetiapine. In short-term placebo-controlled, monotherapy clinical trials with quetiapine extended release that included a discontinuation phase which evaluated discontinuation symptoms, the aggregated incidence of patients experiencing one or more discontinuation symptoms after abrupt cessation was 12.1% (241/1993) for quetiapine extended release and 6.7% (71/1065) for placebo. The incidence of the individual adverse events (i.e., insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability) did not exceed 5.3% in any treatment group and usually resolved after 1 week post-discontinuation. Gradual withdrawal is advised.

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[1] 6 weeks duration

[2] 8 weeks duration

[3] Parameters not measured in the quetiapine registration studies for schizophrenia. Lipid parameters also were not measured in the bipolar mania registration studies.

[4] 13 to 17 years, 6 weeks duration
[5] 10 to 17 years, 3 weeks duration
[6] up to 6 weeks duration
[7] up to 12 weeks duration
[8] up to 3 weeks duration
[9] up to 8 weeks duration
[10] 6 weeks duration
[11] 3 weeks duration
[12] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline. Shifts in total T

ADVERSE REACTIONS

Adults

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The information below is derived from a clinical trial database for quetiapine consisting of over 4300 patients. This database includes 698 patients exposed to quetiapine for the treatment of bipolar depression, 405 patients exposed to quetiapine for the treatment of acute bipolar mania (monotherapy and adjunct therapy), 646 patients exposed to quetiapine for the maintenance treatment of bipolar I disorder as adjunct therapy, and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of quetiapine for the treatment of schizophrenia.

Of these approximately 4300 subjects, approximately 4000 (2300 in schizophrenia, 405 in acute bipolar mania, 698 in bipolar depression, and 646 for the maintenance treatment of bipolar I disorder) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 2400 patient-years. The conditions and duration of treatment with quetiapine varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse reactions during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse reactions without first grouping similar types of reactions into a smaller number of standardized reaction categories.

In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse reactions for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse reactions for bipolar depression.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adults

Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials:

Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse reactions (4% for quetiapine vs. 3% for placebo) in a pool of controlled trials. However,

discontinuations due to somnolence (0.8% quetiapine vs. 0% placebo) and hypotension (0.4% quetiapine vs. 0% placebo) were considered to be drug related [see *Warnings and Precautions* (*5.8* and *5.17*)].

Bipolar Disorder:

Mania: Overall, discontinuations due to adverse reactions were 5.7% for quetiapine vs. 5.1% for placebo in monotherapy and 3.6% for quetiapine vs. 5.9% for placebo in adjunct therapy.

Depression: Overall, discontinuations due to adverse reactions were 12.3% for quetiapine 300 mg vs. 19.0% for quetiapine 600 mg and 5.2% for placebo.

Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials:

In the acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) trials, the most commonly observed adverse reactions associated with the use of quetiapine monotherapy (incidence of 5% or greater) and observed at a rate on quetiapine at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), ALT increased (5%), weight gain (5%), and dyspepsia (5%).

Adverse Reactions Occurring at an Incidence of 1% or More Among Quetiapine Treated Patients in Short-Term, Placebo-Controlled Trials:

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 8 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with quetiapine (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with quetiapine was greater than the incidence in placebo-treated patients.

Table 8. Treatment-Emergent Adverse Reaction Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (Monotherapy)*

Body System/ Preferred Term	Quetiapine (n=719)	Placebo (n=404)
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
Digestive		
Dry Mouth	9%	3%

Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%
Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
Metabolic and Nutritional		
Weight Gain	5%	1%
ALT Increased	5%	1%
AST Increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

In the acute adjunct therapy of bipolar mania (up to 3 weeks) studies, the most commonly observed adverse reactions associated with the use of quetiapine (incidence of 5% or greater) and observed at a rate on quetiapine at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Table 9 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 3 weeks) of acute mania in 1% or more of patients treated with quetiapine (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with quetiapine was greater than the incidence in placebo-treated patients.

Table 9. Treatment-Emergent Adverse Reaction Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)*

Body System/Preferred Term	Quetiapine (n=196)	Placebo (n=203)
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Hormone Level Altered	3%	0%
Heaviness	2%	1%
Infection	2%	1%

Fever	2%	1%
Neck Rigidity	1%	0%
Cardiovascular		
Postural Hypotension	7%	2%
Hypotension	3%	1%
Hypertension	2%	1%
Tachycardia	2%	1%
Hemorrhage	1%	0%
Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Dyspepsia	4%	3%
Increased Appetite	2%	1%
Flatulence	1%	0%
Gastrointestinal Disorder	1%	0%
Endocrine		
Hypothyroidism	2%	1%
Hemic and Lymphatic		
Lymphadenopathy	1%	0%
Metabolic and Nutritional		
Weight Gain	6%	3%
Peripheral Edema	4%	2%
Musculoskeletal		
Twitching	4%	1%
Joint Disorder	1%	0%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Hypertonia	4%	3%
Depression	3%	2%
Speech Disorder	3%	1%
Incoordination	2%	1%
Thinking Abnormal	2%	0%
Anxiety	2%	0%
Ataxia	2%	0%
Respiratory		
Pharyngitis	6%	3%
Rhinitis	4%	2%
Sinusitis	2%	1%
Skin and Appendages		
Sweating	2%	1%
Special Senses		
Amblyopia	3%	2%
Ear Disorder	1%	0%
Ear Pain	1%	0%
Urogenital		

Urinary Tract Infection	2%	1%
Female Lactation	1%	0%
Impotence	1%	0%
Urinary Tract Disorder	1%	0%

In bipolar depression studies (up to 8 weeks), the most commonly observed treatment emergent adverse reactions associated with the use of quetiapine (incidence of 5% or greater) and observed at a rate on quetiapine at least twice that of placebo were somnolence (57%), dry mouth (44%), dizziness (18%), constipation (10%), and lethargy (5%).

Table 10 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 8 weeks) of bipolar depression in 1% or more of patients treated with quetiapine (doses of 300 and 600 mg/day) where the incidence in patients treated with quetiapine was greater than the incidence in placebo-treated patients.

Table 10: Treatment-Emergent Adverse Reaction Incidence in 8-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Depression*

Body System / Preferred Term	**Quetiapine (n=698)**	**Placebo (n=347)**
Cardiac Disorders		
Palpitations	4%	1%
Tachycardia	1%	0%
Eye Disorders		
Vision Blurred	4%	2%
Gastrointestinal Disorders		
Dry Mouth	44%	13%
Constipation	10%	4%
Dyspepsia	7%	4%
Vomiting	5%	4%
Gastroesophageal Reflux Disease	2%	1%
Dysphagia	2%	0%
General Disorders and Administrative Site Conditions		
Fatigue	10%	8%
Asthenia	2%	1%
Injury, Poisoning and Procedural Complications		
Injury	1%	0%
Investigations		
Weight increased	4%	1%
Metabolism and Nutrition Disorders		
Increased Appetite	5%	3%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3%	2%
Pain in Extremity	2%	1%
Nervous System Disorders		
Somnolence†	57%	15%
Dizziness	18%	7%
Lethargy	5%	2%
Akathisia	4%	1%

Extrapyramidal Disorder	3%	1%
Paraesthesia	3%	2%
Dysarthria	3%	0%
Hypersomnia	3%	0%
Tremor	2%	1%
Restless Legs Syndrome	2%	0%
Balance Disorder	2%	1%
Hypoaesthesia	2%	1%
Dystonia	1%	0%
Dizziness, postural	1%	0%
Dyskinesia	1%	0%
Dysgeusia	1%	0%
Psychiatric Disorders		
Irritability	3%	1%
Abnormal Dreams	2%	1%
Confusional State	1%	0%
Respiratory, Thoracic, and Mediastinal Disorders		
Nasal Congestion	5%	3%
Cough	3%	1%
Sinus Congestion	2%	1%
Vascular Disorders		
Orthostatic Hypotension	4%	3%
Hypertension	1%	0%

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse reaction occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Reactions in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Reactions: Spontaneously elicited adverse reaction data from a study of schizophrenia comparing five fixed doses of quetiapine (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse reactions. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse reactions: dyspepsia, abdominal pain, and weight gain.

Adverse Reactions in clinical trials with quetiapine and not listed elsewhere in the label:

The following adverse reactions have also been reported with quetiapine: nightmares, hypersensitivity and elevations in serum creatine phosphokinase (not associated with NMS).

Extrapyramidal Symptoms:

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Adults: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of quetiapine (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with quetiapine treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates

Parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

Table 11: Adverse experiences potentially associated with EPS in a short-term, placebo-controlled multiple fixed-dose Phase III schizophrenia trial (6 weeks duration)

Preferred Term	Placebo (N=51)		Quetiapine 75 mg/day (N=53)		Quetiapine 150 mg/day (N=48)		Quetiapine 300 mg/day (N=52)		Quetiapine 600 mg/day (N=51)		Quetiapine 750 mg/day (N=54)	
	n	%	n	%	n	%	n	%	n	%	n	%
Dystonic event*	4	7.8	2	3.8	2	4.2	0	0.0	2	3.9	3	5.6
Parkinsonism†	4	7.8	2	3.8	0	0.0	1	1.9	1	2.0	1	1.9
Akathisia‡	4	7.8	1	1.9	1	2.1	0	0.0	0	0.0	1	1.9
Dyskinetic event§	0	0.0	2	3.8	0	0.0	0	0.0	1	2.0	0	0.0
Other extraphyrmidal event¶	4	7.8	2	3.8	0	0.0	3	5.8	3	5.9	1	1.9

Parkinsonism incidence rates as measured by the Simpson-Angus total score for placebo and the five fixed doses (75, 150, 300, 600, 750 mg/day) were: -0.6; -1.0, -1.2; -1.6; -1.8 and -1.8. The rate of anticholingergic medication use to treat emergent EPS for placebo and the five fixed doses was: 14%; 11%; 10%; 8%; 12% and 11%.

In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of quetiapine, there were no differences between the quetiapine and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of quetiapine, the incidence of adverse reactions potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse reactions (akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group.

The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups.

Children and Adolescents:

The information below is derived from a clinical trial database for quetiapine consisting of over 1000 pediatric patients. This database includes 677 patients exposed to quetiapine for the treatment of schizophrenia and 393 patients exposed to quetiapine for the treatment of acute bipolar mania.

Incidence of Adverse Reactions in Short-Term, Placebo-Controlled Trials in Children and Adolescents

Adolescents 13 to 17 years of age with Schizophrenia

The following findings were based on a 6-week placebo-controlled trial in which quetiapine was administered in either doses of 400 or 800 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions for quetiapine-treated and placebo-treated patients was 8.2% and 2.7%, respectively. The adverse event leading to discontinuation in 1% or more of patients on quetiapine and at a greater incidence than placebo was somnolence (2.7% and 0% for placebo).

Commonly Observed Adverse Reactions

In therapy for schizophrenia (up to 6 weeks), the most commonly observed adverse reactions associated with the use of quetiapine in adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (34%), dizziness (12%), dry mouth (7%), tachycardia (7%).

Table 12 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during therapy (up to 6 weeks) of schizophrenia in 5% or more of patients treated with quetiapine (doses of 400 or 800 mg/day) where the incidence in patients treated with quetiapine was at least twice the incidence in placebo-treated patients.

Adverse events that were potentially dose-related with higher frequency in the 800 mg group compared to the 400 mg group included dizziness (8.2% vs. 14.9%), dry mouth (4.1% vs. 9.5%), and tachycardia (5.5% vs. 8.1%).

Table 12. Treatment-Emergent Adverse Reaction Incidence in a 6-Week Placebo-Controlled Clinical Trial for the Treatment of Schizophrenia in Adolescent Patients

Body System/Preferred Term	Quetiapine (n=147)	Placebo (n=75)
Central Nervous System Disorders		
Somnolence*	34%	11%
Digestive		
Dry Mouth	7%	1%
Cardiovascular Disorders		
Tachycardia	7%	0%
Nervous System Disorder		
Dizziness	12%	5%

Children and Adolescents 10 to 17 years of age with Bipolar Mania

The following findings were based on a 3-week placebo-controlled trial in which quetiapine was administered in either doses of 400 or 600 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions for quetiapine-treated and placebo-treated patients was 11.4% and 4.4%, respectively. The adverse events leading to discontinuation in 1% or more of patients on quetiapine and at a greater incidence than placebo were somnolence (4.1% vs. 1.1%), fatigue (2.1% vs. 0), irritability (1.6% vs. 0) and syncope (1% vs. 0).

Commonly Observed Adverse Reactions

In bipolar mania therapy (up to 3 weeks) the most commonly observed adverse reactions associated with the use of quetiapine in children and adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (53%), dizziness (18%), fatigue (11%), increased appetite (9%), nausea (8%), vomiting (8%), tachycardia (7%), dry mouth (7%), and weight increased (6%).

Table 13 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse

reactions that occurred during therapy (up to 3 weeks) of bipolar mania in 5% or more of patients treated with quetiapine (doses of 400 or 600 mg/day) where the incidence in patients treated with quetiapine was at least twice the incidence in placebo-treated patients.

Adverse events that were potentially dose-related with higher frequency in the 600 mg group compared to the 400 mg group included somnolence (49% vs. 57%), nausea (6.3% vs. 10.2%) and tachycardia (5.3% vs. 8.2%).

Table 13 Treatment-Emergent Adverse Reaction Incidence in a 3 Week Placebo-Controlled Clinical Trial for the Treatment of Bipolar Mania in Children and Adolescent Patients

Body System/Preferred Term	Quetiapine (n=193)	Placebo (n=90)
Nervous System Disorders		
Somnolence*	53%	14%
Dizziness	18%	2%
Fatigue	11%	4%
Metabolism and Nutrition Disorders		
Increased Appetite	9%	1%
Weight Increased	6%	0%
Gastrointestinal Disorders		
Nausea	8%	4%
Vomiting	8%	3%
Dry Mouth	7%	0%
Cardiac Disorders		
Tachycardia	7%	0%

Adverse Reactions in Schizophrenia and Bipolar Mania Clinical Trials

Commonly Observed Adverse Reactions

In acute therapy for schizophrenia and bipolar mania (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania) the most commonly observed adverse reactions associated with the use of quetiapine in children and adolescents (incidence of 5% or greater and quetiapine incidence at least twice that for placebo) were somnolence (47%), dizziness (15%), fatigue (9%), increased appetite (8%), dry mouth (7%), tachycardia (7%), and weight increased (5%).

Table 14 enumerates the pooled incidence of adverse reactions that occurred during acute therapy of children and adolescents (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania). The table includes only those reactions that occurred in 1% or more of patients treated with quetiapine (doses of 400, 600, or 800 mg/day) and for which the incidence in patients treated with quetiapine was greater than the incidence in patients treated with placebo.

Table 14. Adverse Reactions (incidence ≥ 1% and greater than placebo) in Short-Term, Placebo-Controlled Trials of Children and Adolescents (10 to 17 years of age) with Bipolar Mania or Schizophrenia*

Body System/Preferred Term	Quetiapine (n=340)	Placebo (n=165)
Central/Nervous System Disorder		
Somnolence†	47%	15%
Dizziness	15%	4%

Fatigue	9%	4%
Irritability	4%	1%
Tremor	3%	2%
Akathisia	2%	1%
Syncope	2%	0%
Lethargy	1%	0%
Metabolism and Nutrition Disorders		
Increased Appetite	8%	2%
Weight Increased	5%	1%
Digestive		
Dry Mouth	7%	1%
Cardiovascular Disorders		
Tachycardia	8%	0%
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	3%	1%
Back Pain	2%	1%
Musculoskeletal Stiffness	2%	1%
Respiratory, Thoracic and Mediastinal Disorder		
Nasal Congestion	3%	2%
Gastrointestinal Disorder		
Vomiting	7%	6%
Stomach Discomfort	2%	1%
Skin and Subcutaneous Tissue Disorders		
Acne	2%	1%
General Disorders and Administration Site Conditions		
Pyrexia	2%	1%
Asthenia	2%	1%
Psychiatric Disorders		
Aggression	2%	1%
Restlessness	1%	0%
Eye Disorders		
Vision Blurred	2%	1%
Infections and Infestations		
Tooth Abscess	1%	0%

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% for quetiapine and 5.3% for placebo, though the incidence of the individual adverse events (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% for quetiapine and 1.1% for placebo.

Table 15 below presents a listing of patients with AEs potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia (6-week duration).

Table 15 Adverse experiences potentially associated with EPS in the short-term placebo-controlled monotherapy trial in adolescent patients with schizophrenia

(6-week duration).

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

Table 16 below presents a listing of patients with Adverse Experiences potentially associated with EPS in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration).

Table 16: Adverse experiences potentially associated with EPS in a short-term placebo-controlled monotherapy trial in children and adolescent patients with bipolar mania (3-week duration)

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

Adverse Reactions in Long-Term Open-Label Trial

The adverse reactions reported in a 26-week, open-label trial with quetiapine in 5% or greater of the children and adolescent patients with schizophrenia or bipolar mania were somnolence (30%), headache (19%), vomiting (11%), increased weight (13%), insomnia (8%), nausea (10%), fatigue (8%), dizziness (9%), increased appetite (7%), upper respiratory tract infection (7%), agitation (5%), tachycardia (5%), and irritability (5%).

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 multiple doses $\geq$ 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, and those reaction terms which were so 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 it.

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 (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse 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 increased1, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain[35], 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, dysphagia, 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.

C ardiovascular System: ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

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

Metabolic and Nutritional System: ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand 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[35], vaginitis[35], urinary incontinence, metrorrhagia[35], impotence[35], dysuria, vaginal moniliasis[35], abnormal ejaculation[35], cystitis, urinary frequency, amenorrhea[35], female lactation[35], leukorrhea[35], vaginal hemorrhage[35], vulvovaginitis[35] orchitis[35]; ***Rare:*** gynecomastia[35], nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** 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, thrombocytopenia.

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

Hyperglycemia, hyperlipidemia, weight gain, orthostatic hypotension and changes in thyroid hormone levels have been reported with quetiapine. Increases in blood pressure have also been reported with quetiapine in children and adolescents [see *Warnings and Precautions* (*5.4*, *5.5*, *5.6*, *5.8*, *5.9* and *5.14*)].

Neutrophil Counts

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 $<1.0 \times 10^9$/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 fumarate, compared to 0.1% (2/1349) in patients treated with placebo. Patients with a pre-existing low WBC or a history of drug

induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue quetiapine at the first sign of a decline in WBC in absence of other causative factors [see *Warnings and Precautions* (*5.10*)].

Decreased Hemoglobin

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.

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's potential for inducing orthostatic changes [see *Warnings and Precautions* (*5.8*)].

Children and Adolescents: In the acute (6 week) schizophrenia trial in adolescents, potentially clinically significant 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 (*5.8*)].

In the acute (3 week) bipolar mania trial in children and adolescents, potentially clinically significant increases in heart rate (> 110 bpm) occurred in 1.1% (1/95) of patients receiving quetiapine 400 mg and 2.4% (2/98) 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* (*5.8*)].

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 and galactorrhea.

Other adverse reactions reported since market introduction, which were temporally related to quetiapine therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy, hyponatremia, myocarditis, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Stevens-Johnson syndrome (SJS), and decreased platelets.

In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol), somnambulism (and other related events) and hypothermia have been reported.

[13]Reactions for which the quetiapine incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

[14]Reactions for which the quetiapine incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, nausea, accidental injury, chest pain, face edema, flu syndrome, electrocardiogram abnormal, vomiting, gastritis, SGPT increased, weight loss, nervousness, paresthesia, extrapyramidal syndrome, confusion, cough increased, rash and urinary incontinence.

[15]Reactions for which the quetiapine incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, headache, tinnitus, diarrhea, flatulence, toothache, stomach discomfort, abdominal pain, pyrexia, peripheral edema, nasopharyngitis, influenza, bronchitis, viral gastroenteritis, accidental overdose, decreased appetite, back pain, muscle twitching, myalgia, muscle cramp, headache, insomnia, anxiety, nightmare, libido decreased, suicidal ideation, pollakiuria, dyspnoea, pharyngolaryngeal pain, night sweats and hot flush.

[16]Somnolence combines adverse reaction terms somnolence and sedation.

[17]Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle ridgidity

[18]Patients with the following terms were counted in this category: cogwheel rigidity, tremor

[19]Patients with the following terms were counted in this category: akathisia

[20]Patients with the following terms were counted in this category: tardive dyskinesia, dyskinesia, choreoathetosis

[21]Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder

[22]Somnolence combines adverse event terms somnolence and sedation

[23]Somnolence combines adverse event terms somnolence and sedation

[24]Threshold criteria were applied before rounding to the nearest integer

[25]Somnolence combines adverse event terms somnolence and sedation

[26]Patients with the following terms were counted in this category: nuchal rigidity, hypertonia, dystonia, muscle rigidity

[27]Patients with the following terms were counted in this category: cogwheel rigidity, tremor

[28]Patients with the following terms were counted in this category: akathisia

[29]Patients with the following terms were counted in this category: tardive dyskinesia, dyskinesia, choreoathetosis

[30]Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder

[31]There were no adverse experiences with the preferred term of dystonic or dyskinetic events.

[32]Patients with the following terms were counted in this category: cogwheel rigidity, tremor

[33]Patients with the following terms were counted in this category: akathisia

[34]Patients with the following terms were counted in this category: restlessness; extrapyramidal disorder

[35]adjusted for gender

DRUG INTERACTIONS

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 avoided while taking quetiapine.

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.

The use of quetiapine should be avoided in combination with drugs known to increase QT interval, and caution should be exercised when quetiapine is used in combination with drugs known to cause

electrolyte imbalance [**see Warnings and Precautions** (5.12)].

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.

Phenytoin: Coadministration of quetiapine (250 mg three times daily) and phenytoin (100 mg three times daily) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of quetiapine may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) [see *Dosage and Administration* (*2*)].

Divalproex: Coadministration of quetiapine (150 mg twice daily) and divalproex (500 mg twice daily) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine: Thioridazine (200 mg twice daily) increased the oral clearance of quetiapine (300 mg twice daily) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg three times daily for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg three times daily). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when quetiapine is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, and protease inhibitors).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg twice daily), haloperidol (7.5 mg twice daily), or risperidone (3 mg twice daily) with quetiapine (300 mg twice daily) did not alter the steady-state pharmacokinetics of quetiapine.

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg three times daily dosing.

Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg twice daily) was administered with quetiapine (150 mg twice daily). The mean oral clearance of total valproic acid (administered as divalproex 500 mg twice daily) was increased by 11% in the presence of quetiapine (150 mg twice daily). The changes were not significant.

Lithium: Concomitant administration of quetiapine (250 mg three times daily) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a three times daily schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

USE IN SPECIFIC POPULATIONS

Pregnancy Category C:

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.

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 delivered infants with no major malformations. Among 42 other infants born to pregnant women who used quetiapine during pregnancy, there were no major malformations reported (one study of 36 women, 6 case reports). Due to the limited number of exposed pregnancies, these postmarketing data do not reliably estimate the frequency or absence of adverse outcomes.

When pregnant rats and rabbits were exposed to quetiapine during organogenesis, there was no increase in the incidence of major malformations in fetuses at doses up to 2.4 times the maximum recommended human dose for schizophrenia (MRHD, 800 mg/day on a mg/m^2 basis); however, there was evidence of embryo-fetal toxicity. In rats, delays in skeletal ossification occurred at 0.6 and 2.4 times the MRHD and in rabbits at 1.2 and 2.4 times the MRHD. At 2.4 times the MRHD, there was an increased incidence of carpal/tarsal flexure (minor soft tissue anomaly) in rabbit fetuses and decreased fetal weights in both species. Maternal toxicity (decreased body weights and/or death) occurred at 2.4 times the MRHD in rats and at 0.6 to 2.4 times the MRHD (all doses) 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, 0.12, and 0.24 times the MRHD. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 3.0 times the MRHD.

Non-Teratogenic Effects

Neonates exposed to antipsychotic drugs (including quetiapine), during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Quetiapine was excreted into human milk. It is recommended that women receiving quetiapine fumarate tablets should not breast feed.

In published case reports, the level of quetiapine in breast milk ranged from undetectable to 170 µg/L. The estimated infant dose ranged from 0.09% to 0.43% of the 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).

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%).

Schizophrenia

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

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.

Pediatric use information in patients (13 to 17 years of age) with schizophrenia, and patients (10 to 17 years of age) with bipolar mania is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those patients.

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*) *and Dosage and Administration* (*2*)].

DRUG ABUSE AND DEPENDENCE

Quetiapine is not a controlled substance.

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 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.

OVERDOSAGE

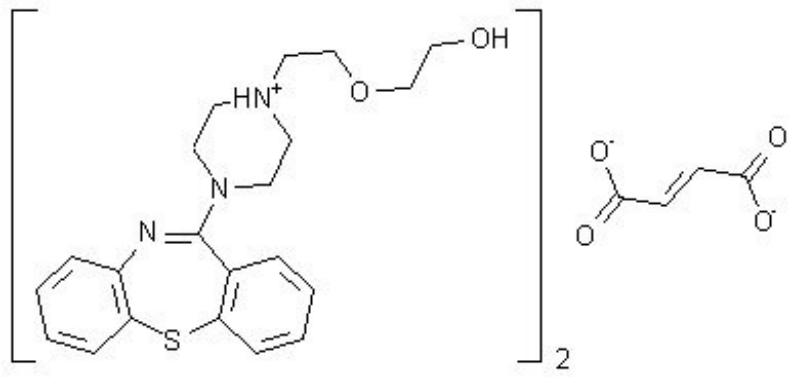
In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed experienced no adverse reactions or recovered fully from the reported reactions. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drugs known pharmacological effects, ie, 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*)]. 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. There were also very rare reports of overdose of quetiapine alone resulting in death or coma.

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.

DESCRIPTION

Quetiapine 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 $C_{42}H_{50}N_6O_4S_2 \bullet C_4H_4O_4$ 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 which is moderately soluble in water.

Quetiapine fumarate tablet is supplied for oral administration as 25 mg (round, pink), 50 mg (round, white to off white), 100 mg (round, yellow), 200 mg (round, white to off white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets.

Inactive ingredients are povidone, dibasic calcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain iron oxide red and iron oxide yellow and the 100 mg and 400 mg tablets contain only iron oxide yellow.

CLINICAL PHARMACOLOGY

The mechanism of action of quetiapine, as with other drugs having efficacy in the treatment of schizophrenia and bipolar disorder, 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 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of quetiapine.

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

Quetiapine's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Quetiapine is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM, respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM, respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). Quetiapine has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

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 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

Pharmacokinetic information in patients (10 to 17 years of age) is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those patients.

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*)].

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.

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*)].

Drug-Drug Interactions

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 P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole [*see Drug Interactions* (*7.1*)].

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam [*see Drug Interactions* (*7.2*)].

NONCLINICAL TOXICOLOGY

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 maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

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

The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of

metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility

Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. 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 150 mg/kg 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 maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. 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 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

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 rats, 75 to 750 mg/kg in mice; these doses are 0.1 to 3.0, and 0.1 to 4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose-related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also 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 any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

CLINICAL STUDIES

Adults

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 III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm 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 inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought

content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

The results of the trials follow:

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of quetiapine (75 mg/day, 150 mg/day, 300 mg/day, 600 mg/day and 750 mg/day given in divided doses three times per day), the 4 highest doses of quetiapine were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 mg/day to 750 mg/day were generally indistinguishable.
2. In a 6-week, placebo-controlled trial (n=286) involving titration of quetiapine in high (up to 750 mg/day given in divided doses three times per day) and low (up to 250 mg/day given in divided doses three times per day) doses, only the high dose quetiapine group (mean dose, 500 mg/day) was superior to placebo on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score.
3. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of quetiapine (450 mg/day given in divided doses both twice daily and three times daily and 50 mg/day given in divided doses twice daily), only the 450 mg/day (225 mg given twice daily) dose group was superior to the 50 mg/day (25 mg given twice daily) quetiapine dose group on the BPRS total score, the BPRS psychosis cluster, and the CGI severity score.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 years compared to those older than 40. The clinical significance of this finding is unknown.

Adolescents (ages 13 to 17)

Clinical trial information in patients (13 to 17 years of age) with schizophrenia is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those adolescent patients.

Manic Episodes

Adults

The efficacy of quetiapine in the acute treatment of manic episodes was established in 3 placebo-controlled trials in patients who met DSM-IV criteria for bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the Young Mania Rating Scale (YMRS) score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of quetiapine with lithium or divalproex.

The primary rating instrument used for assessing manic symptoms in these trials was YMRS, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

Monotherapy

The efficacy of quetiapine in the acute treatment of bipolar mania was established in 2 placebo-

controlled trials. In two 12-week trials (n=300, n=299) comparing quetiapine to placebo, quetiapine was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking quetiapine were dosed in a range between 400 mg/day and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with bipolar mania (YMRS ≥ 20) were randomized to receive quetiapine or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an adequate treatment course of lithium or divalproex prior to randomization. Quetiapine was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score.

The majority of patients in this trial taking quetiapine were dosed in a range between 400 mg/day and 800 mg per day. In a similarly designed trial (n=200), quetiapine was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

Children and Adolescents (ages 10 to 17)

Clinical trial use information in patients (10 to 17 years of age) with bipolar mania is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those pediatric patients.

Depressive Episodes

Adults

The efficacy of quetiapine for the acute treatment of depressive episodes associated with bipolar disorder was established in 2 identically designed 8-week, randomized, double-blind, placebo-controlled studies (N=1045). These studies included patients with either bipolar I or II disorder and those with or without a rapid cycling course. Patients randomized to quetiapine were administered fixed doses of either 300 mg or 600 mg once daily.

The primary rating instrument used to assess depressive symptoms in these studies was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale with scores ranging from 0 to 60. The primary endpoint in both studies was the change from baseline in MADRS score at week 8. In both studies, quetiapine was superior to placebo in reduction of MADRS score. Improvement in symptoms, as measured by change in MADRS score relative to placebo, was seen in both studies at Day 8 (week 1) and onwards. In these studies, no additional benefit was seen with the 600 mg dose. For the 300 mg dose group, statistically significant improvements over placebo were seen in overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q(SF).

Maintenance Treatment as an Adjunct to Lithium or Divalproex

The efficacy of quetiapine in the maintenance treatment of bipolar I disorder was established in 2 placebo-controlled trials in patients (n=1326) who met DSM-IV criteria for bipolar I disorder. The trials included patients whose most recent episode was manic, depressed, or mixed, with or without psychotic features. In the open-label phase, patients were required to be stable on quetiapine plus lithium or divalproex for at least 12 weeks in order to be randomized. On average, patients were stabilized for 15 weeks. In the randomization phase, patients continued treatment with lithium or divalproex and were randomized to receive either quetiapine (administered twice daily totaling 400 mg/day to 800 mg/day) or placebo. Approximately 50% of the patients had discontinued from the quetiapine group by day 280 and 50% of the placebo group had discontinued by day 117 of double-blind treatment. The primary endpoint in these studies was time to recurrence of a mood event (manic, mixed or depressed episode). A mood event was defined as medication initiation or hospitalization for a mood episode; YMRS score ≥20 or MADRS score ≥ 20 at 2 consecutive assessments; or study discontinuation due to a mood event.

In both studies, quetiapine was superior to placebo in increasing the time to recurrence of any mood event. The treatment effect was present for increasing time to recurrence of both manic and depressed episodes. The effect of quetiapine was independent of any specific subgroup (assigned mood stabilizer, sex, age, race, most recent bipolar episode, or rapid cycling course).

HOW SUPPLIED

25 mg Tablets (NDC 16729-145) pink coloured, round, biconvex, film coated tablet, debossed '25' on one side and plain on other side, are supplied in bottles of 30 tablets (NDC 16729-145-10), 100 tablets (NDC 16729-145-01) and 1000 tablets (NDC 16729-145-17).

50 mg Tablets (NDC 16729-146) white to off white, round, biconvex, film coated tablet, debossed '50' on one side and plain on other side, are supplied in bottles of 30 tablets (NDC 16729-146-10), 100 tablets (NDC 16729-146-01) and 1000 tablets (NDC 16729-146-17).

100 mg Tablets (NDC 16729-147) yellow coloured, round, biconvex, film coated tablet, debossed '100' on one side and plain on other side, are supplied in bottles of 30 tablets (NDC 16729-147-10), 100 tablets (NDC 16729-147-01) and 1000 tablets (NDC 16729-147-17).

200 mg Tablets (NDC 16729-148) white to off white round, biconvex, film coated tablet, debossed '200' on one side and plain on other side are supplied in bottles of 30 tablets (NDC 16729-148-10), 100 tablets (NDC 16729-148-00) and 1000 tablets (NDC 16729-148-17).

300 mg Tablets (NDC 16729-149) white to off white, capsule shaped, biconvex, film coated tablet, debossed '300' on one side and plain on other side, are supplied in bottles of 30 tablets (NDC 16729-149-10), 60 tablets (NDC 16729-149-12), 100 tablets (NDC 16729-149-00) and 1000 tablets (NDC 16729-149-17).

400 mg Tablets (NDC 16729-150) yellow coloured, capsule-shaped, biconvex, film coated tablet, debossed '400' on one side and plain on other side, are supplied in bottles of 30 tablets (NDC 16729-150-10), 100 tablets (NDC 16729-150-00) and 500 tablets (NDC 16729-150-16) .

Store at 25ºC (77ºF); excursions permitted to 15 to 30ºC (59 to 86ºF) [See USP].

INFORMATION FOR PATIENTS

[see Medication Guide]

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with quetiapine and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for quetiapine. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking quetiapine.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine is

not approved for elderly patients with dementia-related psychosis [*see Warnings and Precautions* (*5.1*)].

Clinical Worsening and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see Warnings and Precautions* (*5.2*)].

Neuroleptic Malignant Syndrome (NMS)

Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever [*see Warnings and Precautions* (*5.3*)].

Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment [*see Warnings and Precautions* (*5.4*)].

Hyperlipidemia

Patients should be advised that elevations in total cholesterol, LDL-cholesterol and triglycerides and decreases in HDL-cholesterol may occur. Patients should have their lipid profile monitored at the beginning of and periodically during treatment [*see Warnings and Precautions* (*5.5*)].

Weight Gain

Patients should be advised that they may experience weight gain. Patients should have their weight monitored regularly [*see Warnings and Precautions* (*5.6*)].

Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing, which may lead to falls), especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose [*see Warnings and Precautions* (*5.8*)].

Increased Blood Pressure in Children and Adolescents

Blood pressure should be measured at the beginning of, and periodically during, treatment [*see Warnings and Precautions* (*5.9*)].

Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking quetiapine [see *Warnings and Precautions* (*5.10*)].

Interference with Cognitive and Motor Performance

Patients should be advised of the risk of somnolence or sedation (which may lead to falls), especially during the period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery, until they are reasonably certain quetiapine therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine [see *Warnings and Precautions* (*5.17*)].

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see *Warnings and Precautions* (*5.19*)].

Concomitant Medication

As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs [see *Warnings and Precautions* (*5.22*)].

Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised not to breast feed if they are taking quetiapine [*see Use in Specific Populations* (*8.1*) and (*8.3*)].

Need for Comprehensive Treatment Program

Pediatric use information in patients (13 to 17 years of age) with schizophrenia, and patients (10 to 17 years of age) with bipolar mania is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those patients.

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Manufactured By:
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10 8057 0 623125

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SPL MEDGUIDE

MEDICATION GUIDE

Quetiapine fumarate tablets

Read this Medication Guide before you start taking quetiapine fumarate tablets and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about quetiapine fumarate tablets?
Quetiapine fumarate tablets may cause serious side effects, including

1. **Risk of death in the elderly with dementia**
2. **Risk of suicidal thoughts or actions**
3. **High blood sugar (hyperglycemia)**
4. **High fat levels in your blood (increased cholesterol and triglycerides)**
5. **Weight gain**

These serious side effects are described below:

1. **Risk of death in the elderly with dementia:** Medicines like quetiapine fumarate tablets can increase the risk of death in elderly people who have memory loss (dementia). Quetiapine fumarate tablet is not approved for treating psychosis in the elderly with dementia.
2. **Risk of suicidal thoughts or actions (antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions):**
   Talk to your, or your family member's, healthcare provider about:
   - all risks and benefits of treatment with antidepressant medicines.
   - all treatment choices for depression or other serious mental illness.

- **Antidepressant medications may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
- **Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) depression, bipolar illness (also called manic-depressive illness), or suicidal thoughts or actions.
- **How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**
  - Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
  - Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
  - Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- **Never stop an antidepressant medicine without first talking to your healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you

or your family member take. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

3. High blood sugar (hyperglycemia): High blood sugar can happen if you have diabetes already or if you have never had diabetes. High blood sugar could lead to:
1. Build up of acid in your blood due to ketones (ketoacidosis)
2. Coma
3. Death

Increases in blood sugar can happen in some people who take quetiapine fumarate tablets. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes) your healthcare provider should check your blood sugar before you start quetiapine fumarate tablets and during therapy.

Call your doctor if you have any of these symptoms of high blood sugar (hyperglycemia) while taking quetiapine fumarate tablets:
- feel very thirsty
- need to urinate more than usual
- feel very hungry
- feel weak or tired
- feel sick to your stomach
- feel confused, or your breath smells fruity.

4. High fat levels in your blood (increased cholesterol and triglycerides): High fat levels may happen in people treated with quetiapine fumarate tablets. You may not have any symptoms, so your doctor may decide to check your cholesterol and triglycerides during your treatment with quetiapine fumarate tablets.

5. Increase in weight (weight gain): Weight gain is common in people who take quetiapine fumarate tablets so you and your doctor should check your weight regularly. Talk to your doctor about ways to control weight gain, such as eating a healthy, balanced diet, and exercising.

What is a quetiapine fumarate tablet?
- Quetiapine fumarate tablet is a prescription medicine used to treat schizophrenia.
- Quetiapine fumarate tablet is a prescription medicine used to treat bipolar disorder, including:
  - depressive episodes associated with bipolar disorder in adults
  - manic episodes associated with bipolar I disorder alone or with lithium or divalproex in adults
  - long-term treatment of bipolar I disorder with lithium or divalproex in adults
- *Pediatric use information in patients (13 to 17 years of age) with schizophrenia, and patients (10 to 17 years of age) with bipolar mania is approved for AstraZeneca Pharmaceuticals LP's quetiapine fumarate drug product labeling. However, due to AstraZeneca Pharmaceuticals LP's marketing exclusivity rights; this drug product is not labeled for such use in those patients.*

Quetiapine fumarate tablet has not been studied in patients younger than 10 years of age.

What should I tell my healthcare provider before taking quetiapine fumarate tablets?

Before taking quetiapine fumarate tablets, tell your healthcare provider if you have or have had:
- diabetes or high blood sugar in you or your family: your healthcare provider should check your blood sugar before you start quetiapine fumarate tablets and also during therapy
- high levels of total cholesterol, triglycerides or LDL-cholesterol or low levels of HDL-cholesterol
- low or high blood pressure

- low white blood cell count
- cataracts
- seizures
- abnormal thyroid tests
- high prolactin levels
- heart problems
- liver problems
- any other medical condition
- pregnancy or plans to become pregnant. It is not known if quetiapine fumarate tablets will harm your unborn baby
- breast-feeding or plans to breast-feed. Quetiapine can pass into your breast milk. You and your healthcare provider should decide if you will take quetiapine fumarate tablets or breast-feed. You should not do both.

Tell the healthcare provider about all the medicines that you take or recently have taken including prescription medicines, nonprescription medicines, herbal supplements and vitamins.

Quetiapine fumarate tablets and other medicines may affect each other causing serious side effects. Quetiapine fumarate tablets may affect the way other medicines work, and other medicines may affect how quetiapine fumarate tablets works.

Especially tell your healthcare provider if you take or plan to take medicines for:
- depression
- high blood pressure
- Parkinson's disease
- trouble sleeping
- abnormal heart beats or rhythm

Also tell your healthcare provider if you take or plan to take any of these medicines:
- phenytoin, divalproex or carbamazepine (for epilepsy)
- barbiturates (to help you sleep)
- rifampin (for tuberculosis)
- glucocorticoids (steroids for inflammation)
- thioridazine (an antipsychotic)
- ketoconazole, fluconazole or itraconazole (for fungal infections)
- erythromycin (an antibiotic)
- protease inhibitors (for HIV)

This is not a complete list of medicines that can affect or be affected by quetiapine fumarate tablets. Your doctor can tell you if it is safe to take quetiapine fumarate tablets with your other medicines. Do not start or stop any medicines while taking quetiapine fumarate tablets without talking to your healthcare provider first. Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

Tell your healthcare provider if you are having a urine drug screen because quetiapine fumarate tablets may affect your test results. Tell those giving the test that you are taking quetiapine fumarate tablets.

How should I take quetiapine fumarate tablets?
- Take quetiapine fumarate tablets exactly as your healthcare provider tells you to take it. Do not change the dose yourself.
- Take quetiapine fumarate tablets by mouth, with or without food.
- If you feel you need to stop quetiapine fumarate tablets, talk with your healthcare provider first.

If you suddenly stop taking quetiapine fumarate tablets, you may experience side effects such as trouble

sleeping or trouble staying asleep (insomnia), nausea, and vomiting.

- If you miss a dose, take it as soon as you remember. If it is close to the next dose, skip the missed dose. Just take the next dose at your regular time. Do not take 2 doses at the same time unless your healthcare provider tells you to. If you are not sure about your dosing, call your healthcare provider.
- If you take too much quetiapine fumarate tablets, call your healthcare provider or poison control center at 1-800-222-1222 right away or go to the nearest hospital emergency room.

What should I avoid while taking quetiapine fumarate tablets?

Do not drive, operate machinery, or do other dangerous activities until you know how quetiapine fumarate tablets affects you. Quetiapine fumarate tablets may make you drowsy.

- Avoid getting overheated or dehydrated.
  - Do not over-exercise.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun. Do not wear too much or heavy clothing.
  - Drink plenty of water.
- Do not drink alcohol while taking quetiapine fumarate tablets. It may make some side effects of quetiapine fumarate tablets worse.

What are possible side effects of quetiapine fumarate tablets?

Serious side effects have been reported with quetiapine fumarate tablets including:

Also, see "What is the most important information I should know about quetiapine fumarate tablets?" at the beginning of this Medication Guide.

- **Neuroleptic malignant syndrome (NMS):** NMS is a rare but very serious condition that can happen in people who take antipsychotic medicines, including quetiapine fumarate tablets. NMS can cause death and must be treated in a hospital. Call your doctor right away if you become severely ill and have some or all of these symptoms:
- high fever
- excessive sweating
- rigid muscles
- confusion
- changes in your breathing, heartbeat, and blood pressure
- **Tardive dyskinesia:** Tell your healthcare provider about any movements you cannot control in your face, tongue, or other body parts. These may be signs of a serious condition. Tardive dyskinesia may not go away, even if you stop taking quetiapine fumarate tablets. Tardive dyskinesia may also start after you stop taking quetiapine fumarate tablets.
- **Orthostatic hypotension (decreased blood pressure):** lightheadedness or fainting caused by a sudden change in heart rate and blood pressure when rising too quickly from a sitting or lying position.
- **Increases in blood pressure:** reported in children and teenagers. Your healthcare provider should check blood pressure in children and adolescents before starting quetiapine fumarate tablets and during therapy.
- **Low white blood cell count**
- **Cataracts**
- **Seizures**
- **Abnormal thyroid tests:** Your healthcare provider may do blood tests to check your thyroid hormone level.
- **Increases in prolactin levels:** Your healthcare provider may do blood tests to check your prolactin levels.
- **Increases in liver enzymes:** Your healthcare provider may do blood tests to check your liver

enzyme levels.
- **Long lasting and painful erection**
- **Difficulty swallowing**

Common possible side effects with quetiapine fumarate tablets include:

Adults
- drowsiness
- dry mouth
- dizziness
- weakness
- weight gain
- abdominal pain
- constipation
- sore throat
- sluggishness
- upset stomach
- weight gain
- a sudden drop in blood pressure upon standing
- abnormal liver tests

Children and Adolescents:
- drowsiness
- fatigue
- nausea
- dry mouth
- weight gain
- dizziness
- increased appetite
- vomiting
- rapid heart rate

These are not all the possible side effects of quetiapine fumarate tablets. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store quetiapine fumarate tablets?
- Store quetiapine fumarate tablets at room temperature, between 59°F to 86°F (15°C to 30°C).
- Keep quetiapine fumarate tablets and all medicines out of the reach of children.

General information about quetiapine fumarate tablets

Do not take quetiapine fumarate tablets unless your healthcare provider has prescribed it for you for your condition. Do not share quetiapine fumarate tablets with other people, even if they have the same condition. It may harm them.

This Medication Guide provides a summary of important information about quetiapine fumarate tablets. For more information about quetiapine fumarate tablets, talk with your healthcare provider or pharmacist. You can ask your healthcare provider for information about quetiapine fumarate tablets that is written for health professionals.

What are the ingredients in quetiapine fumarate tablets?

Active ingredient: quetiapine fumarate

Inactive ingredients: povidone, dibasic calcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol, and titanium dioxide. The 25 mg tablets contain iron oxide red and yellow. The 100 mg and 400 mg tablets contain only iron oxide yellow.

The symptoms of Schizophrenia include:

- Having lost touch with reality (psychosis)
- Seeing things that are not there or hearing voices (hallucinations)
- Believing things that are not true (delusions)
- Being suspicious (paranoia).

The symptoms of Bipolar Disorder include:

- General symptoms of bipolar disorder include extreme mood swings, along with other specific symptoms and behaviors. These mood swings, or "episodes," include manic (highs) and depressive (lows).
- Common symptoms of a manic episode include feeling extremely happy, being very irritable, restless, talking too fast and too much, and having more energy and needing less sleep than usual.
- Common symptoms of a depressive episode include feelings of sadness or emptiness, increased tearfulness, a loss of interest in activities you once enjoyed, loss of energy, difficulty concentrating or making decisions, feelings of worthlessness or guilt, changes in sleep or appetite.
- Thoughts of death or suicide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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10 8057 0 623125

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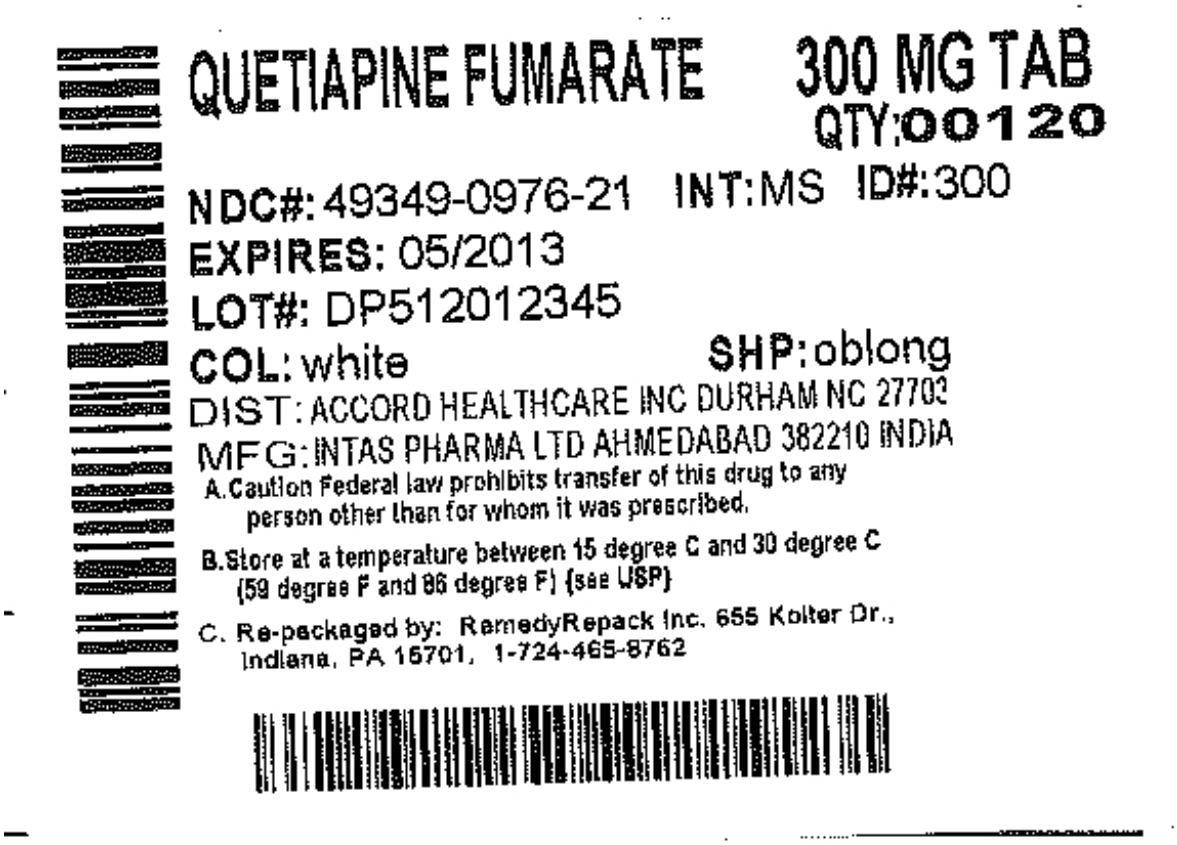
PACKAGE LABEL.PRINCIPAL DISPLAY PANEL SECTION
DRUG: Quetiapine fumarate
GENERIC: Quetiapine fumarate
DOSAGE: TABLET, FILM COATED
ADMINSTRATION: ORAL
NDC: 49349-976-21
STRENGTH:300 mg
COLOR: white
SHAPE: ROUND
SCORE: No score

SIZE: 19 mm
IMPRINT: 120
QTY: 120



QUETIAPINE FUMARATE

quetiapine fumarate tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:49349-976(NDC:16729-145)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
QUETIAPINE FUMARATE (QUETIAPINE)	QUETIAPINE FUMARATE	300 mg

Inactive Ingredients

Ingredient Name	Strength
POVIDONE K12	
DIBASIC CALCIUM PHOSPHATE DIHYDRATE	
CELLULOSE, MICROCRYSTALLINE	

SODIUM STARCH GLYCOLATE TYPE A POTATO	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
HYPROMELLOSES	
POLYETHYLENE GLYCOL 1000000	
TITANIUM DIOXIDE	
FERRIC OXIDE YELLOW	
FERRIC OXIDE RED	

Product Characteristics

Color	white	**Score**	no score
Shape	ROUND (TABLET, FILM COATED)	**Size**	19mm
Flavor		**Imprint Code**	300
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49349-976-21	120 in 1 CANISTER		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202152	02/08/2013	

Labeler - REMEDYREPACK INC. (829572556)

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