PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

PrMINT-QUETIAPINE

quetiapine tablets

Immediate-Release Tablets, 25 mg, 100 mg, 150 mg, 200 mg and 300 mg quetiapine (as quetiapine fumarate), Oral Use

USP

Antipsychotic Agent

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS - Musculoskeletal - Rhabdomyolysis	03/2022
7 WARNINGS AND PRECAUTIONS - Psychiatric	03/2022
7 WARNINGS AND PRECAUTIONS – Skin	11/2021

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

Schizophrenia

MINT-QUETIAPINE (quetiapine fumarate immediate-release) is indicated for:

- the management of the manifestations of schizophrenia.

The antipsychotic efficacy of quetiapine fumarate immediate release was established in short-term (6-week) controlled inpatient trials (see 14 CLINICAL TRIALS). The efficacy of quetiapine fumarate immediate release in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials of patients with manifestations of schizophrenia.

Bipolar Disorder

MINT-QUETIAPINE is indicated as monotherapy for the:

- acute management of manic episodes associated with bipolar disorder.
- acute management of depressive episodes associated with bipolar I and bipolar II disorder.

The efficacy of quetiapine fumarate in bipolar mania was established in two 12-week clinical trials of bipolar patients (see 14 CLINICAL TRIALS). The safety and effectiveness of quetiapine fumarate for long-term use, and for prophylactic use in bipolar mania has not been evaluated.

The efficacy of quetiapine fumarate immediate release in bipolar depression was established in four 8-week clinical trials that included either bipolar I or bipolar II patients (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of quetiapine fumarate immediate release in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use (see 7.1 Special Populations).

1.2 Geriatrics

Geriatrics (>65 years of age): MINT-QUETIAPINE is not indicated in elderly patients with dementia (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7.1 Special Populations**)**.

2. CONTRAINDICATIONS

MINT-QUETIAPINE (quetiapine fumarate immediate-release) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3. SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- **Increased Mortality in Elderly Patients with Dementia**
- **Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo-controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6 fold increase in death rate in the drug-related patients. 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 (see** 7.1.4 Geriatrics - Use in Geriatric Patients with Dementia**).**

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

For considerations in special populations see 4.2 Recommended Dose and Dosage Adjustment - Dosing Considerations in Special Populations.

4.2 Recommended Dose and Dosage Adjustment

Schizophrenia

The usual starting dose of MINT-QUETIAPINE (quetiapine fumarate immediate-release) is 25 mg b.i.d., titrated with increments of 25-50 mg b.i.d. per day, as tolerated, to a target dose of 300 mg/day given b.i.d. within four to seven days.

Further dosage adjustments may be indicated depending on the clinical response and tolerability in the individual patient. Dosage adjustments should generally occur at intervals of not less than 2 days, as steady state for quetiapine fumarate would not be achieved for approximately 1-2 days in the typical patient. When adjustments are necessary, dose increments/decrements of 25-50 mg b.i.d. are recommended.

Clinical trials suggest that the usual effective treatment dose will be in the range of 300-600 mg/day (see 14 CLINICAL TRIALS). However, some patients may require as little as 150 mg/day. In schizophrenia, the safety of doses above 800 mg/day has not been evaluated.

The need for continuing existing EPS medications should be re-evaluated periodically as quetiapine fumarate has not been associated with treatment-emergent EPS across the clinical dose range.

Bipolar Disorder

Bipolar Mania: Usual Dose: The titration rate, based on the clinical trials (see 14 CLINICAL TRIALS) is shown in the table below:

Day	1	2	3	4	5	6
BID	100 mg/day	200 mg/day	300 mg/day	400 mg/day	Up to 600 mg/day	Up to 800 mg/day

Dosage adjustments should be made depending on the clinical response and tolerability in the individual patient.

Approximately 85% of patients responded between 400 and 800 mg/day, while over 50% of patients responded between 600 and 800 mg/day (the average median dose for responders during the last week of treatment was approximately 600 mg/day). In bipolar mania, the safety of doses above 800 mg/day has not been evaluated.

Bipolar Depression: Usual Dose: The titration rate, based on the clinical trials (see 14 CLINICAL TRIALS) is shown in the table below:

Day	1	2	3	4
Once Daily	50 mg/day	100 mg/day	200 mg/day	300 mg/day

Patients in 300 mg fixed dosage arms were continued on quetiapine fumarate immediate release 300 mg/day, from day 4 onward. In clinical trials that had a fixed 600 mg dosage arm, quetiapine fumarate immediate release was further titrated to 400 mg on Day 5 and up to 600 mg by Day 8, depending on clinical response and tolerability of individual patients. Antidepressant efficacy was demonstrated with quetiapine fumarate immediate release at both 300 mg/day and 600 mg/day, however no additional benefit was seen in the 600 mg group during short-term treatment. Thus, a usual target dose of 300 mg/day is recommended.

In bipolar depression, the safety of doses above 600 mg/day has not been evaluated.

MINT-QUETIAPINE should be administered once daily at bedtime.

Dosing Considerations in Special Populations

Pediatric Use: Health Canada has not authorized an indication for pediatric use, as safety and efficacy of MINT-QUETIAPINE in children under the age of 18 years have not been established (see 7.1 Special Populations).

Geriatrics Use: In clinical trials, 38 patients with schizophrenia or related disorders, 65 years of age or over, were treated with quetiapine fumarate immediate release (see 7.1 Special Populations). Given the limited experience with quetiapine fumarate in the elderly, and the higher incidence of concomitant illness and concomitant medication in this population, MINT-QUETIAPINE should be used with caution. The mean plasma clearance of quetiapine fumarate immediate release was reduced by 30% to 50% in elderly subjects when compared to younger patients. The rate of dose titration may thus need to be slower, and the daily therapeutic target dose lower, than that used in younger patients.

Hepatic Impairment: Quetiapine is extensively metabolized by the liver (see 10.3 Pharmacokinetics – Special Populations and Conditions). Therefore, MINT-QUETIAPINE should be used with caution in patients with mild hepatic impairment, especially during the initial dosing period. Patients with mild hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg/day to an effective dose, depending on the clinical response and tolerance in the individual patient. No pharmacokinetic data are available for any dose of quetiapine fumarate immediate release in patients with moderate to severe hepatic impairment. However, should clinical judgement deem treatment with MINT-QUETIAPINE necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS – Hepatic Impairment and 10.3 Pharmacokinetics – Special Populations and Conditions).

Renal Impairment: As clinical experience is lacking, caution is advised (see 7 WARNINGS AND PRECAUTIONS - Renal).

4.4 Administration

MINT-QUETIAPINE is for oral use only.

MINT-QUETIAPINE can be administered with or without food (see 10.3 Pharmacokinetics).

4.5 Missed Dose

If a dose is missed by only a few hours, take it as soon as possible. If most of the day has passed since the missed dose, skip that dose and wait until next scheduled dose. Never take two doses at once.

5. OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

Experience

Clinical Trials: One death has been reported in a clinical trial following an overdose of 13,600 mg of quetiapine alone, however, survival has also been reported in acute overdoses of up to 30,000 mg of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events.

Post-Marketing: In post-marketing experience, there have been cases of coma and death in patients taking a quetiapine fumarate immediate-release overdose. The lowest reported dose associated with coma has been in a patient who took 5,000 mg and had a full recovery within 3 days. The lowest reported dose associated with a death was in a patient who took 6,000 mg.

In post-marketing experience, there were cases reported of QT prolongation with overdose. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. See 7 WARNINGS AND PRECAUTIONS - Hypotension and Syncope.

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects (e.g., drowsiness and sedation, tachycardia, hypotension and anticholinergic effects).

Treatment

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. In this context, published reports in the setting of anticholinergic symptoms describe a reversal of severe central nervous system effects, including coma and delirium, with administration of intravenous physostigmine (1-2 mg), under continuous ECG monitoring. If physostigmine salicylate is used, atropine sulfate should be available to reverse excessive cholinergic effects such as bradycardia, marked salivation, emesis and bronchospasm.

In cases of quetiapine overdose refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade).

Close medical supervision and monitoring should be continued until the patient recovers.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Use	Immediate-Release Tablet 25 mg, 100 mg, 150 mg, 200 mg and 300 mg	The core of the tablet contains: dibasic calcium phosphate dihydrate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The coating of the tablet contains hypromellose, titanium dioxide, macrogol, iron oxide yellow (25 mg, 100 mg and 150 mg tablets), and iron oxide red (25 mg tablets).

MINT-QUETIAPINE (quetiapine fumarate immediate-release) is available as film-coated tablets containing quetiapine fumarate equivalent to 25 mg, 100 mg, 150 mg, 200 mg or 300 mg of quetiapine free base as follows:

25 mg MINT-QUETIAPINE tablets are peach colored, round shaped, biconvex, film coated tablets, debossed with ‘44’ on one side and ‘I’ on the other side, available in HDPE bottles of 100 and 500

tablets.

100 mg MINT-QUETIAPINE tablets are yellow colored, round shaped, biconvex film coated tablets, debossed with '55' on one side and 'I' on the other side, available in HDPE bottles of 100 and 500 tablets.

150 mg MINT-QUETIAPINE tablets are pale yellow colored, round shaped, biconvex, film coated tablets debossed with '46' on one side and 'J' on the other side, available in HDPE bottles of 500 tablets.

200 mg MINT-QUETIAPINE tablets are white to off white colored, round shaped, biconvex, film coated tablets, debossed with '56' on one side and 'I' on the other side, available in HDPE bottles of 100 and 500 tablets.

300 mg MINT-QUETIAPINE tablets are white to off white colored, capsule shaped, biconvex, film coated tablets, debossed with '45' on one side and 'I' on the other side, available in HDPE bottles of 100 and 500 tablets.

7. WARNINGS AND PRECAUTIONS

General

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents (including quetiapine fumarate immediate-release). Appropriate care is advised when prescribing MINT-QUETIAPINE (quetiapine fumarate) for patients who will be experiencing conditions which may contribute to an elevation of core temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. See 8.2 Clinical Trial Adverse Reactions, Pyrexia.

Dependence / Tolerance: There have been reports of quetiapine misuse, abuse, tolerance, and/or physical dependence. These cases include adult and adolescent patients using quetiapine alone or with other substances of abuse. Caution is needed when prescribing quetiapine to patients with a history of alcohol or drug abuse. Patients should be observed closely for signs of MINT-QUETIAPINE misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behaviour), particularly if they have a history of alcohol or drug abuse.

Acute Withdrawal (discontinuation) Symptoms: Acute discontinuation symptoms such as insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability, have been described after abrupt cessation of antipsychotic drugs including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable. Symptoms usually resolved after 1 week post-discontinuation.

Carcinogenesis and Mutagenesis

For animal data, see 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular

Hypotension and Syncope: As with other drugs that have high α_1 adrenergic receptor blocking activity, quetiapine may induce orthostatic hypotension, tachycardia, dizziness, and sometimes syncope, especially during the initial dose titration period. These events may lead to falls (see 8 ADVERSE REACTIONS).

Syncope was reported in 1% (35/4083) of patients treated with quetiapine fumarate, compared with 0.3% (3/1006) on placebo, and 0.4% (2/527) on active control drugs. The risk of hypotension and syncope may be reduced by more gradual titration to the target dose (see 4 DOSAGE AND ADMINISTRATION). MINT-QUETIAPINE should be used with caution in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or other conditions predisposing to hypotension (e.g., dehydration, hypovolemia and treatment with antihypertensive medications) (see 5 OVERDOSAGE).

QT Prolongation: In clinical trials, quetiapine was not associated with a persistent increase in absolute QT intervals. However, the QT effect was not systematically evaluated in a thorough QT study. In post-marketing experience, there have been cases reported of QT prolongation at therapeutic doses in patients with concomitant illness and in patients taking medicines known to cause electrolyte imbalance or increase QT interval, and with overdose (see 5 OVERDOSAGE). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e., the elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalemia, or hypomagnesemia (see 9 DRUG INTERACTIONS).

Cardiomyopathy and Myocarditis: Cardiomyopathy and myocarditis have been reported in clinical trials and in post-marketing experience with quetiapine. These events were temporally related to quetiapine, however a causal relationship has not been established. Treatment should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Endocrine and Metabolism

Worsening of More than one Metabolic Parameter (among Cholesterol and Triglyceride Elevations; Hyperglycemia; Weight Gain): In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.

Cholesterol and Triglyceride Elevations: Very common (≥10%) cases of elevations in serum triglyceride levels (≥2.258 mmol/L on at least one occasion), elevations in total cholesterol (predominantly LDL cholesterol) (≥6.2064 mmol/L on at least one occasion), and decreases in HDL cholesterol (<1.025 mmol/L males; <1.282 mmol/L females at any time) have been observed during treatment with quetiapine in clinical trials (see 8 ADVERSE REACTIONS). Lipid changes should be managed as clinically appropriate.

In short-term placebo-controlled schizophrenia trials, quetiapine fumarate immediate release-

treated patients showed mean increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to mean decreases in the placebo-treated patients. LDL cholesterol was not measured in these trials.

In short-term placebo-controlled bipolar depression trials, quetiapine fumarate immediate release-treated patients had decreases from baseline in mean cholesterol and increases from baseline in mean triglyceride of 0.7% and 12%, respectively, compared to decreases in mean cholesterol and increases in mean triglyceride of 1.8% and 2% respectively for placebo-treated patients.

Hyperglycemia: As with other antipsychotics, hyperglycemia and diabetes mellitus (including exacerbation of pre-existing diabetes, diabetic ketoacidosis, and diabetic coma including some fatal cases) in the aggregate have been reported rarely ($\geq 0.01\%$ - $< 0.1\%$) during the use of quetiapine in post-marketing experience, sometimes in patients with no reported history of hyperglycemia (see 8.5 Post-Market Adverse Reactions).

Increases in blood glucose and hyperglycemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

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 events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients should have baseline and periodic monitoring of blood glucose. Patients 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. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Weight Gain: In controlled schizophrenia clinical trials (up to 6 weeks), mean weight gain was approximately 2.3 kg compared to a mean weight gain of 0.1 kilograms in patients taking placebo (n=427). In open-label extension trials, after 9 to 13 weeks of quetiapine fumarate monotherapy, the mean weight increase was 1.58 kg (n=170), after 14 to 26 weeks, 0.26 kg, after 27 to 39 weeks, 1.66 kg, after 40 to 52 weeks, -1.53 kg, and after 53 to 78 weeks of treatment, the mean weight increase was 1.98 kg (n=137). These data are obtained from uncontrolled, open-label trials; the relevance of these findings to clinical practice is unknown. Weight change over time appeared to be independent of quetiapine dose (see 8 ADVERSE REACTIONS).

In the acute placebo-controlled bipolar mania clinical trials (up to 12 weeks) mean weight gain in patients taking quetiapine fumarate immediate release was 1.8 kg compared to a mean weight loss

of 0.1 kg in patients taking placebo. In patients completing the entire 12 weeks of treatment mean weight gain in patients taking quetiapine fumarate immediate release was 2.8 kg.

In the acute placebo-controlled bipolar depression clinical trials (8 weeks) mean weight gain in patients taking quetiapine fumarate immediate release was 1.15 kg compared to a mean weight gain of 0.1 kg in patients taking placebo. During maintenance treatment, patients treated with quetiapine fumarate immediate release 300 mg or placebo lost on average 0.1 kg and 0.6 kg, respectively, while patients treated with quetiapine fumarate immediate release 600 mg gained on average 0.8 kg. In patients who completed 40 and 54 weeks of maintenance treatment a small mean decrease was seen in the quetiapine fumarate immediate release 300 mg group (-0.2 kg) and placebo group (-0.8 kg) while patients in the quetiapine fumarate immediate release 600 mg group showed a mean weight gain of 1.2 kg (see 8 ADVERSE REACTIONS).

Based on the cumulative acute placebo-controlled clinical trial database, weight gain (based on ≥7% increase in body weight from baseline) was reported in 9.6% in quetiapine-treated patients and 3.8% in placebo-treated patients, which occurs predominantly during the early weeks of treatment in adults (see 8 ADVERSE REACTIONS). Patients should have baseline and periodic monitoring of body weight.

Hyperprolactinemia: During clinical trials with quetiapine, elevation in prolactin levels occurred in 3.6% (158/4416) of patients treated with quetiapine compared to 2.6% (51/1968) on placebo (see 8 ADVERSE REACTIONS).

Increased prolactin levels with quetiapine were observed in rat studies. As is common with compounds which stimulate prolactin release, the administration of quetiapine resulted in an increase in the incidence of mammary neoplasms in rats. The physiological differences between rats and humans with regard to prolactin make the clinical significance of these findings unclear. To date, neither clinical nor epidemiological studies have shown an association between chronic administration of drugs that stimulate prolactin release, and mammary tumourigenesis. Tissue culture experiments, however, indicate that approximately one third of human breast cancers are prolactin dependent *in vitro*; a factor of potential importance if prescription of these drugs is contemplated in a patient with previously detected breast cancer.

Possible manifestations associated with elevated prolactin levels are amenorrhea, galactorrhea, and menorrhagia. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone mineral density in both female and male subjects.

In the multiple fixed-dose schizophrenia clinical trial there were no differences in prolactin levels at study completion for quetiapine fumarate immediate release, across the recommended dose range, and placebo.

Hypothyroidism: Clinical trials in schizophrenia demonstrated that quetiapine fumarate immediate release is associated with a dose-related decrease in total and free thyroxine (T_4). On average quetiapine fumarate immediate release was associated with about a 20% mean reduction in thyroxine levels (both total and free). Forty-two percent of quetiapine fumarate immediate release-treated patients showed at least a 30% reduction in total T_4 and 7% showed at least a 50% reduction. Maximum reduction of thyroxine levels generally occurred during the first two to four weeks of treatment with quetiapine fumarate immediate release. These reductions were maintained

without adaptation or progression during longer term treatment. Decreases in T_4 were not associated with systematic changes in TSH or clinical signs or symptoms of hypothyroidism. Approximately 0.4% (12/2595) of patients treated with quetiapine fumarate immediate release (schizophrenia and bipolar mania studies combined) experienced persistent increases in TSH, and 0.25% of patients were treated with thyroid replacement (see 8 ADVERSE REACTIONS).

Gastrointestinal

Antiemetic Effect: Consistent with its dopamine antagonist effects, quetiapine may have an antiemetic effect. Such an effect may mask signs of toxicity due to overdosage of other drugs, or may mask symptoms of disease such as brain tumour or intestinal obstruction.

Dysphagia and Aspiration Pneumonia: Dysphagia and aspiration have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been established, quetiapine should be used with caution in patients at risk for aspiration pneumonia (see 7.1 Special Populations and 8 ADVERSE REACTIONS).

Constipation and Intestinal Obstruction: Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine. This includes fatal reports in patients who are at a higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation (see 8.5 Post-Market Adverse Reactions). Patients with known or suspected gastrointestinal obstruction (e.g., bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type) may also be at higher risk of intestinal obstruction.

Genitourinary

Priapism: Rare cases of priapism have been reported with antipsychotic use, such as quetiapine fumarate immediate release. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hematologic

Leukopenia, Neutropenia and Agranulocytosis: In clinical trial and post-marketing experience, events of neutropenia, granulocytopenia and agranulocytosis (severe neutropenia with infection) have been reported during antipsychotic use, including quetiapine fumarate immediate release. It is recommended that patients have their complete blood count (CBC) tested prior to starting MINT-QUETIAPINE and then periodically throughout treatment.

Severe neutropenia ($<0.5 \times 10^9$/L) has been uncommonly reported in short-term placebo controlled monotherapy clinical trials with quetiapine. Most of the cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factors(s), or in patients with unexplained fever, and should be managed as clinically appropriate. There have been rare cases of agranulocytosis among all patients treated with quetiapine during clinical trials as well as post-marketing reports (including fatal cases). There have also been cases of agranulocytosis in patients without pre-existing risk

factors. Agranulocytosis has also been reported with other agents in the class (see 8.3 Less Common Clinical Adverse Reactions and 8.5 Post-Market Adverse Reactions).

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 MINT-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 <1 x 10^9/L) should discontinue MINT-QUETIAPINE and have their WBC followed until recovery (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data and 8.5 Post-Market Adverse Reactions).

Venous Thromboembolism: Venous thromboembolism (VTE), including fatal pulmonary embolism, has been reported with antipsychotic drugs, including quetiapine fumarate immediate release, in case reports and/or observational studies. When prescribing MINT-QUETIAPINE all potential risk factors for VTE should be identified and preventative measures undertaken.

Hepatic/Biliary/Pancreatic

Hepatic Impairment: Decreased clearance of quetiapine fumarate immediate release was observed in patients with mild hepatic impairment (see 10.3 Pharmacokinetics - Special Populations and Conditions). Patients with mild hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg/day to an effective dose, depending on the clinical response and tolerability in the individual patient. No pharmacokinetic data are available for any dose of quetiapine fumarate immediate release in patients with moderate or severe hepatic impairment. However, should clinical judgement deem treatment with MINT-QUETIAPINE necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see 10.3 Pharmacokinetics - Special Populations and Conditions and 4 DOSAGE AND ADMINISTRATION).

Transaminase Elevations: During premarketing clinical trials, therapy with quetiapine fumarate immediate release was associated with elevation of hepatic transaminases, primarily ALT. Within a clinical trial database of 1892 quetiapine fumarate immediate release-treated schizophrenia patients, with baseline ALT levels <60 IU/L, 5.3% (101/1892) had treatment-emergent ALT elevations to >120 IU/L, 1.5% (29/1892) had elevations to >200 IU/L, and 0.2% (3/1892) had elevations to >400 IU/L. No patients had values in excess of 800 IU/L. None of the quetiapine fumarate immediate release-treated patients who had elevated transaminase values manifested clinical symptomatology associated with liver impairment. The majority of transaminase elevations were seen during the first two months of treatment. Most elevations were transient (80%) while patients continued on quetiapine fumarate immediate release therapy. Of the 101 quetiapine fumarate immediate release-treated patients whose enzyme levels increased to >120 IU/L, 40 discontinued treatment while their ALT values were still raised. In 114 quetiapine fumarate immediate release-treated patients whose baseline ALT was >90 IU/L, only 1 experienced an elevation to >400 IU/L.

In the bipolar disorder trials, the proportions of patients with transaminase elevations of > 3 times

the upper limits of the normal reference range, was approximately 1% for both quetiapine fumarate immediate release-treated and placebo-treated patients.

Precautions should be exercised when using quetiapine in patients with pre-existing hepatic disorders, in patients who are being treated with potentially hepatotoxic drugs, or if treatment-emergent signs or symptoms of hepatic impairment appear.

Hepatic failure, including fatalities, has also been reported very rarely during the post-marketing period. There have been rare reports of hepatitis in clinical studies. Rare post-marketing reports of hepatitis (with or without jaundice), in patients with or without prior history, have been received. Very rare cases of hepatic steatosis, cholestatic or mixed liver injury have also been reported in the post-marketing period.

For patients who have known or suspected abnormal hepatic function prior to starting quetiapine, standard clinical assessment, including measurement of transaminase levels is recommended. Periodic clinical reassessment with transaminase levels is recommended for such patients, as well as for patients who develop any signs and symptoms suggestive of a new onset liver disorder during quetiapine therapy (see 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data).

Pancreatitis: Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see 7 WARNINGS and PRECAUTIONS - Endocrine and Metabolism), gallstones, and alcohol consumption.

Musculoskeletal

Rhabdomyolysis: Quetiapine may cause rhabdomyolysis at recommended doses, and in the absence of neuroleptic malignant syndrome (NMS). Serious outcomes including compartment syndrome, acute renal failure, and fatalities have been reported. Consider discontinuing quetiapine if markedly elevated creatine kinase concentrations are observed or myopathy is suspected or diagnosed.

Neurologic

Neuroleptic Malignant Syndrome: Neuroleptic Malignant Syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including quetiapine.

The clinical manifestations of NMS are hyperthermia, 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.

In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms. Other important considerations in the

differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system pathology.

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

Tardive Dyskinesia (TD) and Extrapyramidal Symptoms (EPS): Tardive Dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that 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 estimates to predict which patients are likely to develop the syndrome.

In placebo-controlled clinical trials for schizophrenia and bipolar mania the incidence of EPS was no different from that of placebo across the recommended therapeutic dose range. It has been hypothesized that agents with a lower EPS liability may also have a lower liability to produce TD. This relationship predicts that quetiapine should have less potential than typical antipsychotic agents to induce TD in schizophrenia and bipolar mania patients. In short-term, placebo-controlled clinical trials for bipolar depression, the incidence of EPS was higher in quetiapine treated patients than in placebo-treated patients (see 8 ADVERSE REACTIONS).

The risk of developing TD 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.

There is no known treatment for established cases of TD, 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 TD. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that is known to respond to antipsychotic drugs, and 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 TD appear in a patient on quetiapine, dose reduction or drug discontinuation should be considered. Some patients may require treatment with MINT-

QUETIAPINE despite the presence of the syndrome. The symptoms of TD can worsen or even arise after discontinuation of treatment (see 8 ADVERSE REACTIONS).

Seizures: In controlled schizophrenia clinical trials, there was no difference in the incidence of seizures in patients treated with quetiapine or placebo (incidence of 0.4% or 3 events per 100 patient years in patients given quetiapine, compared with 0.5% or 6.9 events per 100 patient years for placebo). Nevertheless, as with other antipsychotics, caution is recommended when treating patients with a history of seizures or with conditions associated with a lowered seizure threshold (see 8 ADVERSE REACTIONS).

Sleep Apnea: There have been post-marketing reports of sleep apnea and related disorders in patients with or without prior history of sleep apnea. In some cases, events were reported to have resolved or improved upon quetiapine fumarate immediate release discontinuation or dose reduction. MINT-QUETIAPINE should be used with caution in patients who have a history of or are at risk for sleep apnea, and/or are receiving concomitant central nervous system (CNS) depressants. In severe cases or if the events continue to persist, MINT-QUETIAPINE dose reduction or gradual discontinuation and alternative therapeutic options should be considered (see 8.5 Post-Market Adverse Reactions).

Anticholinergic (muscarinic) effects:
Urinary Hesitation and Retention: There have been post-marketing reports of urinary retention in quetiapine fumarate immediate release-treated patients with or without prior history. Some patients experiencing severe urinary retention were hospitalized and required catheterization. MINT-QUETIAPINE possesses anticholinergic properties which can lead to adverse drug reactions such as gastric or urinary retention when used alone, at recommended therapeutic doses, or concomitant with other medications with anticholinergic effects, and in the setting of overdose. Therefore, MINT-QUETIAPINE should be prescribed with caution in patients with a current diagnosis or prior history of urinary retention, patients with other risk factors for urinary retention (e.g., benign prostatic hyperplasia [BPH]), conditions predisposing to intestinal obstruction (see 7 WARNINGS AND PRECAUTIONS –Constipation and Intestinal Obstruction) or related gastrointestinal conditions, increased intraocular pressure or narrow angle glaucoma, and patients who are unable to communicate clinical symptoms (e.g., cognitively impaired patients). MINT-QUETIAPINE should also be prescribed with caution in patients receiving medications with anticholinergic activity that can affect voiding. In patients with signs and symptoms of urinary retention, dose reduction or gradual discontinuation of MINT-QUETIAPINE and alternative therapy should be considered (see 8 ADVERSE REACTIONS, 9 DRUG INTERACTIONS, 5 OVERDOSAGE AND 10 CLINICAL PHARMACOLOGY).

Potential Effect on Cognitive and Motor Performance
Somnolence was a very commonly reported adverse event in patients treated with quetiapine, especially during the initial dose titration period. Since quetiapine may cause sedation and impair motor skill, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, until they are reasonably certain that quetiapine therapy does not affect them adversely. Somnolence may lead to falls.

Ophthalmologic

Cataracts: The development of cataracts was observed in association with quetiapine

treatment in chronic dog studies at 4 times the recommended human dose. Lens changes have also been observed in patients during long-term quetiapine fumarate immediate release treatment, but a causal relationship to quetiapine fumarate immediate release use has not been established. The possibility of lenticular changes during long-term use of quetiapine fumarate immediate release in man, thus can not be excluded at this time. Eye examinations (e.g., slit lamp exam) prior to or shortly after initiation of treatment with MINT-QUETIAPINE and at 6 month intervals thereafter, are recommended. If clinically significant lens changes associated with MINT-QUETIAPINE use are observed, discontinuation of MINT-QUETIAPINE should be considered.

Psychiatric

Suicide/ suicidal thoughts or clinical worsening: Depressive episodes are associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission of depression occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. In addition to depressive episodes associated with bipolar disorder, depression may be co-morbid with schizophrenia.

Schizophrenia as well as manic episodes associated with bipolar disorder, can also be associated with an increased risk of suicide-related events, and thus close supervision and appropriate clinical management of high risk patients should accompany drug therapy.

Patients with a history of suicide-related events are also known to be at a greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment.

In placebo-controlled bipolar depression clinical trials with quetiapine fumarate immediate release, the incidence of treatment emergent suicidal ideation or suicidal behaviour, as measured by the Columbia Analysis of Suicidal Behaviour, was 1.5% for quetiapine fumarate immediate release-treated patients and 2.0% for placebo-treated patients.

An FDA meta-analysis of placebo-controlled clinical trials of antidepressant drugs in approximately 4,400 children and adolescents and 77,000 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine.

Renal

There is little experience with quetiapine fumarate immediate release in patients with renal impairment, except in a low (subclinical) single dose study (see 10.3 Pharmacokinetics - Special Populations and Conditions). MINT-QUETIAPINE should thus be used with caution in patients with known renal impairment, especially during the initial dosing period (see 4 DOSAGE AND ADMINISTRATION).

Skin
Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), toxic

epidermal necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are potentially life threatening adverse drug reactions that have been reported during quetiapine exposure. SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Discontinue quetiapine if severe cutaneous adverse reactions occur.

7.1 Special Populations

7.1.1 Pregnant Women

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with quetiapine. The safety and efficacy of quetiapine during human pregnancy have not been established. Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported.

MINT-QUETIAPINE should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

7.1.2 Breast-feeding

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of quetiapine fumarate immediate release in pediatric patients have not been established; therefore, Health Canada has not authorized an indication for pediatric use.

Weight gain has been observed with atypical antipsychotic use in pediatric and adolescent patient populations. Independent of any drug-specific effects, weight gain can be associated with adverse changes in other metabolic parameters (e.g., glucose and lipid metabolism). Abnormal childhood weight and metabolic status can have adverse effects on cardiovascular outcomes in adulthood. Weight gain and adverse effects on other metabolic parameters associated with atypical antipsychotics can be more frequent or more severe in pediatric and adolescent patients than in the adult patients.

Increased blood pressure (not seen in adults) occurs more frequently in quetiapine treated patients than in placebo in patients under the age of 18 years. Additionally, frequency categories for increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope were higher in patients under the age of 18 years treated with quetiapine than in adults. Increased appetite, elevations in serum prolactin, and vomiting were very common in children and adolescents, and common in adults. Rhinitis and syncope were common in children and adolescents, and uncommon in adults (see 8.2.1 Clinical Trial Adverse Reactions - Pediatrics).

Long-term safety data including cardiometabolic effects, growth, maturation and behavioural development in patients under 18 years of age has not been systematically evaluated.

Neonates: Neonates exposed to antipsychotic drugs including MINT-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.

7.1.4 Geriatrics

Geriatrics (≥ 65 years of age): The number of patients 65 years of age or over, with schizophrenia or related disorders, exposed to quetiapine fumarate immediate release, during clinical trials was limited (n=38). When compared to younger patients the mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly subjects. In addition, as this population has more frequent hepatic, renal, central nervous system, and cardiovascular dysfunctions, and more frequent use of concomitant medication, caution should be exercised with the use of quetiapine in the elderly patient (see 4 DOSAGE AND ADMINISTRATION).

Use in Geriatric Patients with Dementia

Overall Mortality: Elderly patients with dementia related psychosis treated with atypical antipsychotic drugs are at an increased risk of death. In a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs, elderly patients with dementia treated with atypical antipsychotic drugs, which included quetiapine fumarate immediate release, showed increased mortality compared to placebo.

In two placebo-controlled trials with oral quetiapine in this population, the incidence of mortality was 5.5% for quetiapine-treated patients compared to 3.2% for placebo-treated patients.

MINT-QUETIAPINE is not indicated for the treatment of elderly patients with dementia-related psychosis.

Cerebrovascular adverse events: An increased risk of cerebrovascular adverse events has been seen in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. There is insufficient data with quetiapine to know if there is an increased risk of cerebrovascular events associated with quetiapine. An increased risk, however, cannot be excluded. MINT-QUETIAPINE is not indicated in patients with dementia.

Vascular disease: Quetiapine should be used with caution in patients with risk factors for stroke or with a history of stroke.

Dysphagia: 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 (see 7 WARNINGS AND

PRECAUTIONS - Gastrointestinal and 8 ADVERSE REACTIONS).

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

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

The most commonly reported adverse drug reactions in both clinical trials and during post-marketing experience with quetiapine (≥10%) are somnolence dizziness, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use. The figures cited 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 populations studied.

Adverse Events Associated with Discontinuation

Short-Term Placebo-Controlled Clinical Trials:

Schizophrenia: Overall, 3.9% of quetiapine fumarate immediate-release treated patients (n=510) discontinued treatment due to adverse events compared with 2.9% of placebo treated patients (n=206). Somnolence, the single most common adverse event leading to withdrawal from quetiapine treatment, led to the withdrawal of four quetiapine-treated patients and no placebo-treated patients. Postural hypotension, hypotension, and/or tachycardia led to withdrawal of 1.8% of quetiapine-treated subjects, compared to 0.5% of placebo-treated subjects.

Bipolar Disorder:

Bipolar Mania: Discontinuations due to adverse events were similar for quetiapine fumarate immediate release (5.7%) and placebo (5.1%).

Bipolar Depression: Discontinuations due to adverse events were 13.1% for quetiapine fumarate immediate release and 6.3% for placebo. Sedation, somnolence and dizziness were the most common adverse events leading to discontinuation in the quetiapine fumarate immediate release treatment groups.

Combined Short- and Long-term Controlled Trial Database in Schizophrenia: In a premarketing controlled clinical trial database of 1710 quetiapine fumarate immediate release-treated patients, 5% discontinued due to an adverse event. Somnolence was the single most common adverse event leading to withdrawal of 24 patients from quetiapine fumarate immediate release, and was the only adverse event leading to withdrawal that occurred in more than 1% of patients. Cardiovascular adverse events (e.g., postural hypotension, hypotension, tachycardia, dizziness) accounted for 20% of all subject withdrawals from quetiapine treatment. Sixteen (0.9%) quetiapine-treated subjects were withdrawn due to elevated liver enzymes. Four quetiapine-treated subjects were withdrawn because of leucopenia. Two of these subjects had at least one clinically significant, non-baseline low neutrophil count. Two quetiapine-treated subjects were withdrawn from the trial because of suspected neuroleptic malignant syndrome (NMS).

Commonly Observed Adverse Events in Short-Term Placebo-Controlled Clinical Trials

Schizophrenia: The following treatment-emergent adverse events, derived from Table 1, commonly occurred during acute therapy with quetiapine fumarate immediate release (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo): somnolence, dizziness, dry mouth, postural hypotension, and elevated ALT levels.

Bipolar Disorder:
***Bipolar Mania*:** In the bipolar mania studies, the following treatment-emergent adverse events commonly occurred during acute therapy with quetiapine fumarate immediate release (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo): somnolence, dry mouth, and weight gain.

Bipolar Depression: In the bipolar depression studies, the following treatment-emergent adverse events commonly occurred during acute therapy with quetiapine fumarate immediate release (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo): dry mouth, somnolence, sedation, dizziness and constipation.

Incidence of Adverse Events in Placebo-Controlled Clinical Trials

Certain portions of the discussion below relating to objective or numeric safety parameters are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania trials. However, this information is also generally applicable to bipolar mania. Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in 1% or more of patients treated with quetiapine fumarate immediate release (doses of 150 mg/day or more) where the incidence in patients treated with quetiapine fumarate immediate release was greater than the incidence in placebo-treated patients.

Table 1 Adverse Events Reported for at least 1% of Quetiapine Fumarate immediate release-Treated Subjects (Doses ≥150 mg/day) and for a Higher Percentage of Quetiapine Fumarate immediate release-Treated Subjects than Subjects Who Received Placebo in Short-Term, Placebo-Controlled Schizophrenia Phase II-III Trials

Body system and COSTART Term	Percentage of subjects with adverse*	
	quetiapine fumarate immediate release (n = 449)	Placebo (n = 202)
Whole body		
Headache	20	17
Abdominal pain	4	1
Back pain	2	1
Fever	2	1
Nervous system		
Somnolence	18	11
Dizziness	10	4
Digestive system		
Constipation	9	5
Dry mouth	7	2
Dyspepsia	6	2
Gamma glutamyl transpeptidase increased	2	1
Cardiovascular system		
Postural hypotension	8	2
Tachycardia	7	5
Palpitation	1	0
Metabolic and nutritional disorders		
ALT increased	7	2
AST increased	4	1
Weight gain	2	0
Endocrine system		
Hypothyroidism	1	0
Skin and appendages		
Rash	4	3
Respiratory system		
Rhinitis	3	1
Hemic and lymphatic system		
Leucopenia	2	0
Special senses		
Ear pain	1	0

*Subjects may have had more than one adverse event.

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (8 weeks) of bipolar depression in ≥1% of patients treated with quetiapine fumarate immediate release (doses of 300 or 600 mg/day) where the incidence in patients treated with quetiapine fumarate immediate release was greater than the incidence in placebo-treated patients.

Table 2 Adverse Events Reported for at least 1% of Quetiapine Fumarate immediate release-Treated Subjects (Doses of 300 or 600 mg/day) and for a Higher Percentage of Quetiapine Fumarate immediate release-Treated Subjects than Subjects Who Received Placebo in 8-Week Placebo-Controlled Bipolar Depression Phase III Trials

Body System and MedDRA Preferred Term[a]	Percentage of subjects with adverse events*	
	quetiapine fumarate immediate release (n = 1712)	Placebo (n = 602)
General disorders		
Fatigue	7	5
Irritability	2	1
Asthenia	2	1
Nervous system disorders		
Somnolence	22	6
Sedation	18	6
Dizziness	14	6
Akathisia	3	1
Lethargy	3	1
Tremor	2	1
Paresthesia	2	1
Hypersomnia	2	0
Extrapyramidal disorder	2	1
Dysarthria	2	0
Restless legs syndrome	1	0
Dysgeusia	1	0
Gastrointestinal disorders		
Dry mouth	29	9
Constipation	8	3
Dyspepsia	4	3
Dysphagia	1	0
Cardiac disorders		
Palpitations	3	1
Tachycardia	2	0
Orthostatic hypotension	2	1
Metabolism and nutritional disorders		
Increased appetite	4	2
Weight increased	3	1
Musculoskeletal and connective tissue		
Arthralgia	2	1
Respiratory disorder		
Nasal congestion	3	1
Cough	2	1
Special senses		
Vision blurred	3	1

*Events for which quetiapine fumarate immediate release incidence was equal to or less than placebo are not listed in the table. Table reports percentage rounded to the nearest integer.

[a]Patients with multiple events falling under the same preferred term are counted only once in that term.

Other Adverse Events

Weight Gain: Based on the cumulative acute placebo-controlled clinical trial database, weight gain (based on ≥7% increase in body weight from baseline) was reported in 9.6% in quetiapine-treated patients and 3.8% in placebo-treated patients, which occurs predominantly during the early weeks of treatment in adults. See 7 WARNINGS AND PRECAUTIONS - Weight Gain).

Somnolence: Somnolence may occur, usually during the first two weeks of treatment, which generally resolves with the continued administration of quetiapine.

Vital Signs: As with other antipsychotics with α_1 adrenergic blocking activity, quetiapine may induce postural hypotension, associated with very common cases of dizziness, common cases of tachycardia and, in uncommon cases, some patients may experience syncope especially during the initial dose titration period (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular). In placebo-controlled clinical trials in schizophrenia, postural hypotension was reported with an incidence of 8% in quetiapine fumarate immediate release-treated patients compared to 2% in placebo-treated patients. quetiapine fumarate immediate release was associated with a mean baseline to endpoint increase in heart rate of 3.9 beats per minute, compared to 1.6 beats per minute among placebo-treated patients.

Dyspnea: Common cases of dyspnea often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.

Palpitations: Common cases of palpitations have occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.

Peripheral Edema: As with other antipsychotic agents, common cases of peripheral edema have been reported in patients treated with quetiapine.

Pyrexia: There have been common cases of pyrexia in patients treated with quetiapine.

Vomiting: There have been common cases of vomiting in patients treated with quetiapine although this has been seen more often in elderly patients (>65 years of age).

Mild Asthenia: As with other antipsychotic agents, common cases of mild asthenia have been reported in patients treated with quetiapine.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant quetiapine fumarate immediate release /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 fumarate immediate release compared to 0.6% (1/156) incidence for placebo. Quetiapine fumarate immediate release 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 may be related to the potential of quetiapine for inducing orthostatic changes (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular). In bipolar mania trials, the proportion of patients meeting the

criteria for tachycardia was 0.5% (1/192) for quetiapine fumarate immediate release compared to 0% (0/178) for placebo. In bipolar depression trials, the proportion of patients meeting the criteria for tachycardia in the acute phase was 0.06% (1/1704) for quetiapine fumarate immediate release compared to 0% (0/598) for placebo.

During maintenance treatment, the proportion was 0.4% (1/278) compared to 0.4% (1/284) for placebo.

Extrapyramidal Symptoms (EPS): There have been very common cases of EPS reported. Table 3 enumerates the percentage of patients with treatment-emergent extrapyramidal symptoms in a short-term acute phase clinical trial in patients with schizophrenia comparing five fixed doses of quetiapine fumarate immediate release with placebo (n = ~ 50 patients per group), as assessed by: 1) spontaneous complaints of parkinsonism (extrapyramidal syndrome, hypertonia, tremor and cogwheel rigidity), or akathisia; 2) Simpson-Angus scores (mean change from baseline); and 3) use of anticholinergic medication to treat emergent EPS.

Table 3 Treatment-Emergent Extrapyramidal Symptoms, Assessed By Spontaneous Reports, Simpson Scale, And Incidence Of Anticholinergic Use

	placebo	QUETIAPINE FUMARATE immediate release				
		75 mg	150 mg	300 mg	600 mg	750 mg
Spontaneous Reports of Parkinsonian Symptoms*	10%	6%	4%	4%	8%	4%
Spontaneous Reports of Akathisia	8%	2%	2%	0%	0%	2%
Simpson Scale	- 0.6	-1.0	- 1.2	- 1.6	- 1.8	- 1.8
Incidence of Anticholinergic Use	14%	11%	10%	8%	12%	11%

*Patients may have had more than one Parkinsonism adverse event

There were no differences between the quetiapine fumarate immediate release and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics and no evidence of dose-related increase in EPS or in the use of concomitant anticholinergics across the dose range of 75 – 750 mg/day.

In 2 bipolar mania placebo-controlled clinical trials using variable doses of quetiapine fumarate immediate release, there were no differences between the quetiapine fumarate immediate release and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores and Barnes Akathisia rating scale, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

In short-term placebo-controlled clinical trials in schizophrenia and bipolar mania, the aggregated incidence of EPS-related adverse events was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). In short-term placebo-controlled clinical trials in bipolar depression, the aggregated incidence of EPS-related adverse events was 8.9% for quetiapine compared to 3.8% for placebo. The incidence of individual EPS-related adverse events (e.g., akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity), however was generally low and did not exceed 4% for any individual adverse event. In long-term studies of schizophrenia and bipolar disorder the aggregated exposure adjusted

incidence of treatment-emergent EPS was similar between quetiapine and placebo (see 7 WARNINGS AND PRECAUTIONS - Neurologic).

Blurred Vision: There have been common cases of blurred vision in patients administered quetiapine.

Dysarthria: There have been common cases of dysarthria in patients administered quetiapine.

Acute Withdrawal (discontinuation) Symptoms: Acute discontinuation symptoms such as insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability, have been described after abrupt cessation of antipsychotic drugs including quetiapine fumarate immediate release. Gradual withdrawal over a period of at least one to two weeks is advisable. Symptoms usually resolved after 1 week post-discontinuation (see 7 WARNINGS AND PRECAUTIONS - General).

Abnormal dreams and nightmares: There have been common cases of abnormal dreams and nightmares in patients administered quetiapine.

Suicide-related events: In short-term placebo-controlled clinical trials across all indications and ages, the incidence of suicide-related events (suicidal thoughts, self-harm and suicide) was 0.8% for both quetiapine (76/9327) and for placebo (37/4845).

In these trials of patients with schizophrenia the incidence of suicide-related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥25 years of age.

In these trials of patients with bipolar mania the incidence of suicide-related events was 0% for both quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both quetiapine (6/496) and placebo (6/503) in patients ≥25 years of age.

In these trials of patients with bipolar depression the incidence of suicide-related events was 3.0% (7/233) for quetiapine and 0% (0/120) for placebo in patients 18-24 and 1.2% for both quetiapine (19/1616) and placebo (11/622) in patients ≥25 years of age (See 7 WARNINGS AND PRECAUTIONS).

Irritability: There have been common cases of irritability in patients administered quetiapine.

Increased appetite: There have been common cases of increased appetite in patients administered quetiapine.

Constipation: Patients should be advised of the risk of severe constipation during MINT-QUETIAPINE treatment, and that they should tell their doctor if constipation occurs or worsens, as they may need laxatives.

8.2.1 Clinical Trial Adverse Reactions - Pediatrics

The safety and efficacy of quetiapine fumarate immediate release in children under the age of 18 years have not been established and its use is not recommended.

The same adverse drug reactions described above for adults should be considered for children and adolescents. The following table summarizes adverse drug reactions that occur in a higher frequency category in children and adolescents patients (ages 10-17 years) than in the adult population or adverse drug reactions that have not been identified in the adult population, based on data for formulations containing quetiapine (see 7.1 Special Populations).

Table 4 Adverse Drug Reactions in Children and Adolescents[a]

Body System and MedDRA Term	Percentage of Subjects With Adverse events	
	quetiapine fumarate (n=340)[b]	Placebo (n=165)[b]
Metabolic and nutritional disorders		
Increased appetite	7.6	2.4
Investigations		
Prolactin[c]	13.4 (Male) 8.7 (Female)	4.0 (Male) 0.0 (Female)
Increases in blood pressure[d]	15.2 (Systolic) 40.6 (Diastolic)	5.5 (Systolic) 24.5 (Diastolic)
Gastrointestinal disorders		
Vomiting	6.5	5.5
Respiratory, thoracic, and mediastinal disorders		
Rhinitis	0.3	0.6
Nervous system disorders		
Syncope	1.5	0.0

[a] Based on pooled data from schizophrenia and mania pediatric placebo-controlled studies

[b] For the term increase in blood pressure, the "n" for the quetiapine fumarate immediate release arm was 335 and for the Placebo arm, was 163.

[c] Prolactin levels (patients <18 years of age): >20 µg/L males; >26 ug/L females at any time. Less than 1% of patients had an increase to a prolactin level 100 µg/L

[d] Based on shifts above clinically significant thresholds (adapted from the National Institute of Health criteria) or increases >20 mmHg for systolic or >10mmg for diastolic blood pressure at any time in two acute weeks (3-6 weeks) placebo-controlled trials in children or adolescents.

Weight Gain in Children and Adolescents

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine fumarate immediate release group and -0.4 kg in the placebo group. Twenty one percent of quetiapine fumarate immediate release treated patients and 7% of placebo-treated patients gained ≥ 7 % of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine fumarate immediate release group and 0.4 kg in the placebo group. Twelve percent of quetiapine fumarate

immediate release treated patients and 0% of placebo-treated patients gained ≥ 7% of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine fumarate immediate release. 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 fumarate immediate release met this criterion after 26 weeks of treatment.

In one 8-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar depression, the mean increase in body weight was 1.4 kg in the quetiapine fumarate extended release tablets group and 0.6 kg in the placebo group. 13.7 % of quetiapine fumarate extended release-treated patients and 6.8% of placebo-treated patients gained ≥ 7 % of their body weight.

Cumulatively, 17% of quetiapine treated children and adolescents gained ≥ 7% of their body weight versus 2.5% of placebo treated in these studies. In contrast, 9.6% of adults treated with quetiapine gained ≥ 7% of their body weight versus 3.8% of placebo treated based on the cumulative acute placebo-controlled clinical trial database.

Extrapyramidal Symptoms in Children and Adolescent Population

Across the placebo-controlled studies, the incidences of adverse events potentially related to extrapyramidal symptoms for adolescents and children in both schizophrenia and bipolar mania were higher in quetiapine treated patients, a finding that was not observed in trials of adults with these indications.

In a short-term placebo-controlled monotherapy trial in adolescent patients (13-17 years of age) with schizophrenia, the aggregated incidence of extrapyramidal symptoms was 12.9% for quetiapine fumarate immediate release and 5.3% for placebo, though the incidence of the individual adverse events (e.g., akathisia, tremor, extrapyramidal disorder, hypokinesia, restlessness, psychomotor hyperactivity, muscle rigidity, dyskinesia) was generally low and did not exceed 4.1% in any treatment group. In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar mania, the aggregated incidence of extrapyramidal symptoms was 3.6% for quetiapine fumarate immediate release and 1.1% for placebo.

In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10-17 years of age) with bipolar depression, the aggregated incidence of extrapyramidal symptoms was 1.1% for quetiapine fumarate extended release and 0.0% for placebo.

Cholesterol and Triglyceride Elevations: Very common (≥10%) cases of elevations in serum triglyceride levels (≥1.69 mmol/L on at least one occasion), elevations in total cholesterol (predominantly LDL cholesterol) (≥5.172 mmol/L on at least one occasion) have been observed during treatment with quetiapine in patients <18 years of age in clinical trials.

Increased Blood Pressure: 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 fumarate immediate release 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 fumarate immediate release 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.

Suicide Related Events: Although not indicated, in clinical trials in patients <18 years of age with schizophrenia, the incidence of suicide-related events was 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo.

Although not indicated, in clinical trials in patients <18 years of age with bipolar mania, the incidence of suicide-related events was 1.0% (2/193) for quetiapine and 0% (0/90) for placebo.

Although not indicated, there has been one trial conducted in patients 10-17 years of age with bipolar depression. The incidence of suicide related events was 1.0% (1/92) for quetiapine and 0% (0/100) for placebo. In this study there were two additional events in two patients that occurred during an extended post-treatment follow-up phase of the study; one of these patients was on quetiapine at the time of the event.

8.3 Less Common Clinical Trial Adverse Reactions

Seizures: There have been uncommon reports of seizures in patients administered quetiapine, although the frequency was no greater than that observed in patients administered placebo in controlled clinical trials (see 7 WARNINGS AND PRECAUTIONS - Neurologic).

Restless Legs Syndrome: There have been uncommon cases of restless legs syndrome in patients administered quetiapine.

Priapism: There have been rare reports of priapism in patients administered quetiapine.

Somnambulism: In rare cases, somnambulism and other related events, such as sleep-related eating disorder, have been reported.

Neuroleptic Malignant Syndrome: As with other antipsychotics, rare cases of neuroleptic malignant syndrome have been reported in patients treated with quetiapine (see 7 WARNINGS AND PRECAUTIONS - Neurologic).

Hypothermia: There have been rare cases of hypothermia in patients treated with quetiapine.

Bradycardia: Uncommon cases of bradycardia and related events have been reported in patients treated with quetiapine. It may occur at or near initiation of treatment and be associated with hypotension and/or syncope.

Pancreatitis: Rare cases of pancreatitis have been reported from a review of all clinical trials with quetiapine.

Rhinitis: Uncommon cases of rhinitis have been reported.

Hypersensitivity: Uncommon cases of hypersensitivity including angioedema have been reported.

Tardive Dyskinesia: There have been uncommon cases of tardive dyskinesia reported in patients administered quetiapine (see 7 WARNINGS AND PRECAUTIONS - Neurologic).

Dysphagia: There have been uncommon cases of dysphagia in patients administered quetiapine. In clinical trials an increase in the rate of dysphagia with quetiapine versus placebo was only observed in bipolar depression (see 7 WARNINGS AND PRECAUTIONS - Gastrointestinal and 7.1 Special Populations).

Urinary retention: There have been uncommon cases of urinary retention in patients administered quetiapine.

Agranulocytosis: There have been rare cases of agranulocytosis based on the frequency of patients during all quetiapine clinical trials with severe neutropenia ($<0.5 \times 10^9$/L) and infection.

Rhabdomyolysis: There have been very rare cases of rhabdomyolysis in patients administered therapeutic doses of quetiapine.

Confusional state: There have been uncommon cases of confusional state in patients administered quetiapine.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

As with other antipsychotics, common cases of leucopenia and/or neutropenia have been observed in patients administered quetiapine. In clinical trial and post-marketing experience, events of severe neutropenia ($<0.5 \times 10^9$/L), granulocytopenia and agranulocytosis (severe neutropenia and infection) have been reported during antipsychotic use, including quetiapine fumarate immediate release (see 10 CLINICAL PHARMACOLOGY). Leucopenia cases were based on shifts from normal baseline to potentially clinically important values at anytime post-baseline in all trials. Shifts in white blood cells were defined as $\leq 3 \times 10^9$ cells/L at any time (see 7 WARNINGS AND PRECAUTIONS - Hematologic). Based on shifts (eosinophil shifts were defined as $\geq 1 \times 10^9$ cells/L at any time) from normal baseline to potentially clinically important values at anytime post-baseline in all trials, common cases of increased eosinophils have been observed. Uncommon cases of thrombocytopenia (platelet count decreased, $\leq 100 \times 10^9$/L on at least one occasion) have been observed.

Decreased hemoglobin to ≤130 g/L males, ≤120 g/L females on at least one occasion occurred in 11% of quetiapine patients in all trials including open-label extensions. In short-term placebo-controlled trials, decreased hemoglobin to ≤130 g/L males, ≤120 g/L females on at least one occasion occurred in 8.3% of quetiapine patients compared to 6.2% of placebo patients.

Based on clinical trial adverse event reports not associated with neuroleptic malignant syndrome, rare cases of elevations in blood creatine phosphokinase have been reported in patients

administered quetiapine.

Hyperprolactinemia: Common cases of elevations in serum prolactin levels have been observed (>20 µg/L in males and >30 µg/L in females) (see 7 WARNINGS AND PRECAUTIONS - Hyperprolactinemia).

Neutropenia: In all short-term placebo-controlled monotherapy clinical trials among patients with a baseline neutrophil count ≥ 1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count <1.5 x 10^9/L was 1.9% in patients treated with quetiapine, compared to 1.5% in placebo-treated patients. The incidence ≥0.5 - <1.0 x 10^9/L was 0.2% in patients treated with quetiapine and 0.2% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count <1.0 x 10^9/L, among patients with a baseline neutrophil count ≥1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count <0.5 x 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo-treated patients (see 7 WARNINGS AND PRECAUTIONS - Hematologic).

Transaminase Elevations: Common cases of asymptomatic elevations (shift from normal to >3 times the upper limits of normal at any time) in serum alanine aminotransferase (ALT) or gamma-GT levels have been observed in some patients administered quetiapine. Uncommon cases of asymptomatic elevations (shift from normal to >3 times the upper limits of normal at any time) in serum aspartate aminotranferase (AST) have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment (see 7 WARNINGS AND PRECAUTIONS - Hepatic/Biliary/Pancreatic).

Thyroid: Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. Based on shifts (total T_4, free T_4, total T_3 and free T_3 <0.8 x LLN (pmol/L) and TSH >5mIU/L at anytime) from normal baseline to a potentially clinically important value at anytime post-baseline in all trials, uncommon cases of decreases in free T_3 and common cases of decreases in total T_4, free T_4 and total T_3 as well as increases in TSH have been reported. Table 5 shows the incidence of these shifts in short-term placebo-controlled clinical trials.

Table 5 Incidence of potentially clinically significant shifts in thyroid hormone levels and TSH in short term placebo-controlled clinical trials*

Total T4		Free T4		Total T3		Free T3		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)

* Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline. Shifts in total T4, free T4, total T3 and free T3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.

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 and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T_4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first 6 weeks of quetiapine treatment, with no further

reduction during long-term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. In 8 patients, where TBG was measured, levels of TBG were unchanged (see 7 WARNINGS AND PRECAUTIONS - Endocrine and Metabolism).

Hyperglycemia: Blood glucose increases to hyperglycemic levels (fasting blood glucose ≥7.0 mmol/L or a non-fasting blood glucose ≥11.1 mmol/L on at least one occasion) have been observed commonly (≥1% - <10%) with quetiapine in clinical trials (see 7 WARNINGS AND PRECAUTIONS - Hyperglycemia).

In 2 long-term bipolar maintenance placebo-controlled adjunct clinical trials, mean exposure 213 days for quetiapine fumarate immediate release (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level (≥7.0 mmol/L) for patients more than 8 hours since a meal was 18.0 per 100 patient years for quetiapine fumarate immediate release (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6% of patients).

In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 treated with quetiapine and 1490 treated with placebo), the percent of patients who had a fasting blood glucose ≥7.0 mmol/L or a non-fasting blood glucose ≥11.1 mmol/L was 3.5% for quetiapine and 2.1% for placebo.

In a 24 week trial (active-controlled, 115 patients treated with quetiapine fumarate immediate release) 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 ≥11.1 mmol/L was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥7.0 mmol/L was 2.6% (see 7 WARNINGS AND PRECAUTIONS - Endocrine and Metabolism).

Cholesterol and Triglyceride Elevations: Very common (≥10%) cases of elevations in serum triglyceride levels (≥2.258 mmol/L on at least one occasion), elevations in total cholesterol (predominantly LDL cholesterol) (≥6.2064 mmol/L on at least one occasion), and decreases in HDL cholesterol levels (<1.025 mmol/L males; <1.282 mmol/L females at any time) have been observed during treatment with quetiapine in clinical trials (see 7 WARNINGS AND PRECAUTIONS - Cholesterol and Triglyceride Elevations). Lipid changes should be managed as clinically appropriate.

In one 24-week clinical trial, where LDL cholesterol was directly measured as opposed to calculated, there was a slight mean increase in total cholesterol in patients administered quetiapine fumarate immediate release, which was driven by increases in LDL cholesterol. The mean LDL level increased at Week 24 by 10% in patients administered quetiapine fumarate immediate release, which was statistically significant. The total cholesterol/HDL ratio did not change significantly during therapy with quetiapine fumarate immediate release. Furthermore, triglycerides did not increase significantly nor did HDL cholesterol decrease during therapy. See 7 WARNINGS AND PRECAUTIONS - Cholesterol and Triglyceride Elevations.

8.5 Post-Market Adverse Reactions

The following adverse reactions were identified during post approval use of quetiapine fumarate

immediate release. 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.

During post-marketing experience, leucopenia and/or neutropenia have been reported during quetiapine fumarate immediate release treatment. Resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine fumarate immediate release. Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leucopenia and/or neutropenia. In post-marketing reports, there have been cases of agranulocytosis (including fatal cases) in patients administered quetiapine (see 7 WARNINGS AND PRECAUTIONS - Hematologic).

Drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP) and erythema multiforme (EM) have been reported with unknown frequency (see 7 WARNINGS AND PRECAUTIONS - Skin).

As with other antipsychotics, hyperglycemia and diabetes mellitus (including exacerbation of pre-existing diabetes, diabetic ketoacidosis, and diabetic coma including some fatal cases) in the aggregate have been reported rarely (≥0.01% - <0.1%) during the use of quetiapine fumarate immediate release, sometimes in patients with no reported history of hyperglycemia (see 7 WARNINGS AND PRECAUTIONS - Endocrine and Metabolism).

Anaphylactic reactions have been reported very rarely in post-marketing reports, including a case with a fatal outcome, possibly related to quetiapine fumarate immediate release treatment. The reporting rate of anaphylaxis associated with quetiapine fumarate immediate release use, which is generally accepted to be an underestimate due to underreporting, does not exceed the background incidence rate estimates. Estimates of the background incidence rate (all cause) of severe life-threatening anaphylaxis in the general population range between 80 and 210 cases per million person-years, and the incidence rate of drug-induced anaphylaxis is reported to be 16 cases per million person-years. In addition, the all cause fatal anaphylaxis rate is reported to be one case per million person-years while the drug-induced fatal anaphylaxis is estimated to be 0.3 cases per million person-years. If a patient develops anaphylaxis after treatment with quetiapine, the drug should be discontinued and an alternative treatment started.

In patients who have a history of or are at risk for sleep apnea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be prescribed with caution.
Based on post-marketing reports, galactorrhea has been reported rarely.

During post-marketing experience, there have been cases of intestinal obstruction (ileus) in patients administered quetiapine (see 7 WARNINGS AND PRECAUTIONS – Gastrointestinal).

Although there have been post-marketing cases of neonatal withdrawal in mothers administered quetiapine, the frequency is unknown (see 7.1 Special Populations).

In post-marketing reports, there have been cases of urinary retention in patients administered quetiapine (see 7 WARNINGS AND PRECAUTIONS – Anticholinergic (muscarinic) effects).

Hepatic failure, including fatalities, has been reported very rarely during the post-marketing period.

Rare post-marketing reports of hepatitis (with or without jaundice), in patients with or without prior history, have been received. Very rare cases of hepatic steatosis, cholestatic or mixed liver injury have also been reported in the post-marketing period (see 7 WARNINGS AND PRECAUTIONS - Hepatic/ Biliary/Pancreatic).

During post-marketing experience, there have been cases of cutaneous vasculitis casually associated with quetiapine, with a frequency of "Not known".

Musculoskeletal: Post-market cases of rhabdomyolysis have been causally associated with quetiapine. See 7 WARNINGS AND PRECAUTIONS – Rhabdomyolysis.

Other adverse reactions reported since market introduction, which were temporally related to quetiapine therapy, but not necessarily causally related include the following: cardiomyopathy, myocarditis (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular) and syndrome of inappropriate secretion of antidiuretic hormone (SIADH).

9. DRUG INTERACTIONS

9.2 Drug Interactions Overview

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

Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval (see 7 WARNINGS AND PRECAUTIONS - Cardiovascular).

Urinary Hesitation and Retention: Caution should be exercised in prescribing MINT-QUETIAPINE (immediate-release) to patients who are receiving other medications that have anticholinergic (muscarinic) properties and may affect voiding (see 7 WARNINGS AND PRECAUTIONS - (Anticholinergic (muscarinic) effects).

9.3 Drug-Behavioural Interactions

Alcohol: Quetiapine fumarate immediate release potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with psychotic disorders. Alcoholic beverages should be avoided while taking quetiapine.

9.4 Drug-Drug Interactions

The Effect of Quetiapine Fumarate immediate release on Other Drugs

Antihypertensive Agents: Because of its potential for inducing hypotension, quetiapine may enhance the effects of certain antihypertensive agents.

Levodopa and Dopamine Agonists: As it exhibits in vitro dopamine antagonism, quetiapine may antagonize the effects of levodopa and dopamine agonists.

Lithium: The single dose pharmacokinetics of lithium were not altered when coadministered with quetiapine fumarate immediate release.

Antipyrine: Quetiapine fumarate immediate release did not induce the hepatic enzyme systems involved in the metabolism of antipyrine.

Lorazepam: Quetiapine fumarate immediate release did not affect the single dose pharmacokinetics of lorazepam.

Divalproex: Co-administration of quetiapine fumarate immediate release (150 mg bid) and divalproex (500 mg bid) increased the mean oral clearance and the mean maximum plasma concentration of total valproic acid (administered as divalproex) by 11%. These changes were not clinically relevant.

The Effect of Other Drugs on Quetiapine Fumarate immediate release

Hepatic Enzyme Inducers: Concomitant use of quetiapine with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, and hence, in each patient, consideration for a higher dose of quetiapine, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of MINT-QUETIAPINE (quetiapine fumarate immediate release) is 800 mg/day and continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient.

Co-administration of quetiapine and another microsomal enzyme inducer, phenytoin, caused five-fold increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g., barbiturates, rifampicin, etc.).

The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g., sodium valproate).

CYP 3A4 inhibitors: CYP 3A4 is the primary enzyme responsible for cytochrome P450-mediated metabolism of quetiapine. Thus, coadministration of compounds (such as ketoconazole, erythromycin, clarithromycin, diltiazem, verapamil, or nefazodone), which inhibit CYP 3A4, may increase the concentration of quetiapine. In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of quetiapine of 235% and 522%, respectively, with a corresponding decrease in mean oral clearance of 84%. The mean half-life of quetiapine increased from 2.6 to 6.8 hours, but the mean t_{max} was unchanged. Due to the potential for an interaction of a similar magnitude in a clinical setting, the dosage of quetiapine should be reduced during concomitant use of quetiapine and potent CYP 3A4 inhibitors

(such as azole antifungals, macrolide antibiotics, and protease inhibitors). Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

Divalproex: Co-administration of quetiapine fumarate immediate release (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine by 17% without changing the mean oral clearance.

Cimetidine: In a clinical study examining the pharmacokinetics of quetiapine fumarate immediate release following coadministration with cimetidine, (a non-specific P450 enzyme inhibitor), no clinically significant interaction was observed.

Thioridazine*:* Coadministration of thioridazine (200 mg b.i.d.) with quetiapine fumarate immediate release (300 mg b.i.d.), increased the clearance of quetiapine fumarate immediate release by 65%.

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Fluoxetine (60 mg daily), imipramine (75 mg b.i.d.), haloperidol (7.5 mg b.i.d.), and risperidone (3 mg b.i.d.) did not significantly alter the steady state pharmacokinetics of quetiapine.

9.5 Drug-Food Interactions

MINT-QUETIAPINE can be administered with or without food.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

10. CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

MINT-QUETIAPINE (quetiapine fumarate immediate-release), a dibenzothiazepine derivative, is an antipsychotic agent. Quetiapine and the active plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of quetiapine fumarate immediate release is not known.

10.2 Pharmacodynamics

Quetiapine: Quetiapine exhibits affinity for brain serotonin $5HT_2$ and $5HT_{1A}$ receptors (*in vitro*, Ki = 288 and 557 nM, respectively), and dopamine D_1 and D_2 receptors (*in vitro*, Ki = 558 and 531

nM, respectively). It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2 receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal symptoms (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine also has high affinity for histamine H_1 receptors (*in vitro*, Ki = 10 nM) and adrenergic α_1 receptors (*in vitro*, Ki = 13 nM), with a lower affinity for adrenergic α_2 receptors (*in vitro*, Ki = 782 nM), but no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors and at the norepinephrine reuptake transporter (NET).

Quetiapine is active in pharmacologic tests for antipsychotic activity, such as conditioned avoidance in primates. It also reverses the actions of dopamine agonists measured either behaviourally or electrophysiologically in mice, rats, cats and monkeys. Quetiapine also elevates levels of the dopamine metabolites homovanillic acid (HVA) and 3,4 dihydroxyphenylalanine (DOPAC) in brain, which are considered to be neurochemical indices of dopamine D_2 receptor blockade. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of quetiapine fumarate immediate release in humans is not known.

In preclinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2 receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarization blockade of the A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

Norquetiapine: Norquetiapine similar to quetiapine, exhibits affinity for brain serotonin $5HT_2$ and $5HT_{1A}$ receptors (*in vitro*, Ki = 2.9 nM and 191 nM, respectively), and dopamine D_1 and D_2 receptors (*in vitro*, Ki = 42 nM and 191 nM respectively). Additionally, like quetiapine, norquetiapine also has high affinity at histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 receptors. Contrary to quetiapine, norquetiapine exhibits high affinity for NET and has moderate to high affinity for several muscarinic receptor subtypes. This contributes to adverse drug reactions reflecting anticholinergic effects when quetiapine is used at therapeutic doses, when used concomitantly with other medications that possess anticholinergic effects, and in the setting of overdose. See Anticholinergic (muscarinic) effects.

Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to the therapeutic efficacy of quetiapine as an antidepressant; however, the clinical relevance of these interactions has not been established. Although affinity at $5HT_{2B}$ has been observed for norquetiapine, norquetiapine is found to be an antagonist and not an agonist at the receptor.

10.3 Pharmacokinetics

The pharmacokinetics of quetiapine and norquetiapine are linear within the clinical dose range. The kinetics of quetiapine are similar in men and women, and smokers and non- smokers.

Absorption: Quetiapine is well absorbed following oral administration. In studies with radiolabelled drug, approximately 73% of the total radioactivity is recovered in the urine and 21% in the faeces over a period of one week. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%,

respectively. Peak plasma concentrations of quetiapine generally occur within 2 hours after oral administration. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

Distribution: Quetiapine has a mean apparent volume of distribution of 10±4 L/kg, and is approximately 83% bound to plasma proteins.

Metabolism: Quetiapine is extensively metabolized by the liver, with parent compound accounting for less than 5% of the dose in the urine and faeces, one week following the administration of radiolabelled quetiapine. Since quetiapine is extensively metabolised by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients.

Major routes of metabolism of quetiapine involve oxidation of the alkyl side chain, hydroxylation of the dibenzothiazepine ring, sulphoxidation, and phase 2 conjugation. The principal human plasma metabolites are the sulfoxide, and the parent acid metabolite, neither of which are pharmacologically active.

In vitro investigations established that CYP 3A4 is the primary enzyme responsible for cytochrome P450-mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 -fold higher than those observed at a dose range of 300 to 800 mg/day in humans.

Quetiapine and several of its metabolites (including norquetiapine) have been tested in vitro for their affinity for $5HT_2$, D_1 and D_2 receptors, and in vivo animal models. The major metabolites, parent acid and sulfoxide, are pharmacologically inactive in plasma. The 7-hydroxy and 7-hydroxy N-dealkylated metabolites are pharmacologically active with in vitro binding comparable to or greater than that for parent compound. The peak plasma concentrations for the 7 -hydroxy and 7-hydroxy N-dealkylated metabolites account for approximately only 5% and 2% of that of quetiapine at steady state, respectively.

Elimination: The elimination half-life of quetiapine is approximately 6-7 hours upon multiple dosing within the proposed clinical dosage range. The elimination half- life of norquetiapine is approximately 12 hours. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special Populations and Conditions

- **Geriatrics (≥ 65 years of age):** The mean clearance of quetiapine in the elderly is approximately 30 to 50% of that seen in adults aged 18-65 years (see 7.1 Special Populations and 4 DOSAGE AND ADMINISTRATION).

- **Hepatic Impairment:** In 8 cirrhotic subjects with mild hepatic impairment, administration of a single 25 mg (sub-clinical) oral dose of quetiapine fumarate immediate release resulted in

a 40% increase in both AUC and C_{max}. Clearance of the drug decreased by 25% whereas $t_{1/2}$ was elevated by nearly 45%. Therefore, MINT-QUETIAPINE should be used with caution in patients with mild hepatic impairment, especially during the initial dosing period. No pharmacokinetic data are available for any dose of quetiapine fumarate immediate release in patients with moderate or severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS - Hepatic Impairment and 4 DOSAGE AND ADMINISTRATION).

- **Renal Impairment:** At single low (sub-clinical) doses, the mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 mL/min/1.73 m^2). However, the individual clearance values remained within the range observed for healthy subjects (see 7 WARNINGS AND PRECAUTIONS – Renal and 4 DOSAGE AND ADMINISTRATION).

11. STORAGE, STABILITY AND DISPOSAL

MINT-QUETIAPINE (quetiapine fumarate immediate-release) should be stored between 15°C – 30°C.

12. SPECIAL HANDLING INSTRUCTIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

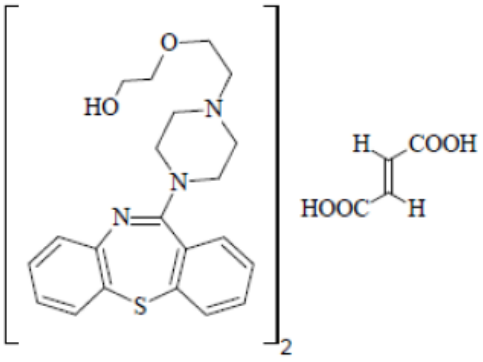
Drug Substance

Proper name: quetiapine fumarate

Chemical name: Bis[2-(2-[4-(dibenzo[b,f][1,4]thiazepin-11-yl)piperazin-1-yl] ethoxy)ethanol] fumarate (IUPAC)

Molecular formula and molecular mass: $C_{42}H_{50}O_4N_6S_2$. $C_4H_4O_4$; 883.1 g/mol

Structural formula:



Physicochemical properties:
Description: Quetiapine fumarate is a white to off-white powder. It is only very slightly soluble in ether, slightly soluble in water, and soluble in 0.1 N HCl

Ionization Constant: pKa1 = 6.83 in phosphate buffer at 22°C
pKa2 = 3.32 in formic buffer at 22°C

Partition Coefficient: Log P = 0.45 (octanol/water)

Melting Point: 172.0°C - 174°C

14. CLINICAL TRIALS

14.1 Clinical Trials by Indication

Schizophrenia

The efficacy of quetiapine fumarate immediate-release in the short-term management of schizophrenia was demonstrated in 3 short-term (6-week) controlled trials of inpatients who met a DSM-III-R diagnosis of schizophrenia.

Study Results:

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of quetiapine fumarate immediate release (75, 150, 300, 600 and 750 mg/day on a t.i.d. schedule), the 4 highest doses of quetiapine fumarate immediate release 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 to 750 were generally indistinguishable. Quetiapine fumarate immediate release, at a dose of 300 mg/day, was superior to placebo on the SANS.

2. In a 6-week, placebo-controlled trial (n=286) involving titration of quetiapine fumarate immediate release in high (up to 750 mg/day on a t.i.d. schedule) and low (up to 250 mg/day on a t.i.d. schedule) doses, only the high dose quetiapine fumarate immediate release group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score and the SANS.

3. In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of quetiapine fumarate immediate release (450 mg/day on both b.i.d. and t.i.d. schedules and 50 mg/day on a b.i.d. schedule), only the 450 mg/day (225 mg b.i.d. schedule) dose group was generally superior to the 50 mg/day (25 mg b.i.d.) quetiapine fumarate immediate release dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Clinical trials have demonstrated that quetiapine fumarate immediate release is effective when given twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours. This is further supported by the data from a positron emission tomography (PET) study which identified that for quetiapine, $5HT_2$ and D_2 receptor occupancy is maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

Bipolar Disorder

Bipolar Mania

The efficacy of quetiapine fumarate immediate release in the treatment of manic episodes was established in two 12 week placebo-controlled monotherapy trials in patients who met DSM-IV criteria for Bipolar I disorder. These trials included patients with or without psychotic features and excluded patients with rapid-cycling and mixed episodes. There were from 95 to 107 patients per treatment group in each study.

The primary rating instrument used for assessing manic symptoms in these trials was the Young Mania Rating Scale (YMRS), and these studies included patients with a wide range of baseline YMRS scores (i.e. 18 to 58). The primary outcome in these trials was change from baseline in the YMRS total score at Day 21.

Study Results: In the two 12-week trials comparing quetiapine fumarate immediate release to placebo, quetiapine fumarate immediate release was significantly superior to placebo in

reducing manic symptoms. Of those patients with a clinical response, 87% received doses of quetiapine fumarate immediate release between 400 and 800 mg per day; in the two individual studies, 52% and 81% of responders received doses between 600 and 800 mg per day (b.i.d. dosing).

Bipolar Depression

The efficacy of quetiapine fumarate immediate release for the management of depressive episodes associated with bipolar disorder was established in four 8-week placebo-controlled trials (n=2593). These clinical trials included patients with either bipolar I or bipolar II disorder with or without a rapid cycling course.

The primary endpoint was the change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 8.

Study Results: In all four trials, quetiapine fumarate immediate release at 300 mg/day and 600 mg/day was demonstrated to be statistically significant versus placebo in reducing depressive symptoms. The antidepressant effect of quetiapine fumarate immediate release was statistically significant at Week 1 (for three of the studies), Week 2 (for all four studies) and maintained throughout 8 weeks of treatment.

Sixty-four percent (64%) of quetiapine fumarate immediate release treated patients had at least a 50% improvement in MADRS total score compared to 46% of the placebo-treated patients ($p<0.001$). The proportion of patients showing a MADRS total score ≤12 (remitters) was 62% for quetiapine fumarate immediate release compared to 42% for placebo ($p<0.001$).

There were fewer episodes of treatment-emergent mania with either dose of quetiapine fumarate immediate release (3.0%) than with placebo (5.0%).

14.3 Comparative Bioavailability Studies

A blinded, two-sequence, single dose, crossover bioequivalence study was conducted between 1 x 25 mg MINT-QUETIAPINE (quetiapine fumarate, Mint Pharmaceuticals Inc.) and 1 x 25 mg SEROQUEL® (quetiapine fumarate, AstraZeneca Canada Inc.) in 43 healthy adult male and female human study participants under fasting conditions. The results are presented below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Quetiapine Fumarate Tablets (1 x 25 mg) From measured data Geometric Mean Arithmetic Mean (%CV)				
Pharmacokinetic Parameter	Test*	Reference†	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (hr*ng/mL)	448.25 482.82 (41.23%)	420.23 466.73 (47.54%)	106.69	101.49 - 112.16
AUC_I (hr*ng/mL)	466.42 504.38 (42.44%)	435.74 485.82 (48.34%)	107.05	101.79 - 112.58
C_{max} (ng/mL)	106.77 117.31 (48.17%)	98.52 116.38 (66.02%)	108.96	99.69 - 119.10
T_{max}§ (hr)	0.830 (0.50 - 3.50)	0.850 (0.50 - 4.00)		
$T_{½}$@ (hr)	6.17 (18.78%)	5.54 (23.34%)		

* MINT-QUETIAPINE (quetiapine fumarate 25 mg tablets) of Mint Pharmaceuticals Inc.
† PrSEROQUEL® (quetiapine fumarate 25 mg tablets) of AstraZeneca Canada Inc., purchased in Canada
§ Expressed as the median (range) only
@ Expressed as the Arithmetic mean (%CV) only

15. MICROBOLOGY

No microbiological information is required for this drug product.

16. NON-CLINICAL TOXICOLOGY

General Toxicology

Thyroid: 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 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 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.

Cataracts: 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.

Acute Toxicity: Single dose studies were conducted in mice and rats by the oral and intraperitoneal routes and in dogs by the oral route. The principal clinical signs in mice, rats and dogs of decreased motor activity, ptosis, loss of righting reflex, tremors, ataxia, prostration and convulsions were consistent with the pharmacological activity of the drug. The lowest oral doses causing lethality were 250 mg/kg in mouse and 500 mg/kg in rat; no deaths occurred at the highest oral dose tested (750 mg/kg) in dogs. The highest parenteral non-lethal doses were 100 mg/kg in both mouse and rat.

Subacute/Chronic Toxicity: In multiple dose studies in rats, dogs and monkeys (refer to Table 6 for individual study details) anticipated central nervous system effects of an antipsychotic drug were observed with quetiapine (e.g., sedation at lower doses and tremor, convulsions or prostration at higher exposures).

Hyperprolactinemia, induced through the dopamine D_2 receptor antagonist activity of quetiapine or its metabolites, varied between species, but was most marked in the rat. A range of effects consequent to this were seen in the 12 month study including mammary hyperplasia, increased pituitary weight, decreased uterine weight and enhanced growth of females.

Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey.

Thyroid follicular cell hypertrophy and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey.

Pigmentation of a number of tissues, particularly the thyroid, was not associated with any morphological or functional effects.

Transient increases in heart rate, unaccompanied by an effect on blood pressure, occurred in dogs.

Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in cynomolugus monkeys dosed up to 225 mg/kg/day, or in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man.

No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies.

Mutagenicity

Genetic toxicity studies with quetiapine show that it is not a mutagen or a clastogen. There was no evidence of mutagenic potential in reverse (*Salmonella typhimurium* and *E. coli*) or forward point mutation (CHO-HGPRT) assays or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the rat bone marrow erythrocyte micronucleus assay).

Carcinogenicity

Results from the 2 year carcinogenicity studies performed in mice and rats (and mouse sighting studies) are summarized in Table 7.

In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinemia.

In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.

Reproductive and Developmental Toxicology

Results from the individual reproduction and teratology studies, performed with quetiapine in rats and rabbits, are summarized in Table 8.

Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction.

Quetiapine had no teratogenic effects.

Table 6: Principal Multiple Dose Toxicity Studies with Quetiapine

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Rat Hla:(SD)/BR	oral gavage	4 weeks dosing and 4 weeks withdrawal	14	0 25 50 150	Ptosis at all doses. Body weight gain decreased at 150 mg/kg/day. Liver weight was increased and uterus, spleen and pituitary weights were decreased in all dose groups. Epididymis and heart weight was decreased at 150 mg/kg/day. Deciduoma-metrial gland changes at 50 mg/kg/day.
Rat Hla:(SD)BR	oral gavage	6 months dosing and 4 weeks withdrawal	29	0 25 50 150	Ptosis at all doses. Reduced body weight gain at 50 mg/kg/day and 150 mg/kg/day. Plasma TSH increased and T_3 reduced at 150 mg/kg/day. Pigment deposition and hypertrophy of thyroid follicular cells at 50 mg/kg/day and 150 mg/kg/day. In all dose groups, mammary gland hypertrophy/hyperplasia, atrophy and/or mucification of cervical/vaginal mucosa. Liver weight increased at all doses with hepatocellular vacuolation at 150 mg/kg/day. No adverse-effect dose level was 25 mg/kg.
Rat Crl:(WI)BR	oral gavage	12 months of dosing then 5 weeks withdrawal	20	0 10 25 75 250	Hypoactivity and hyperprolactinemia and sequelae (all doses). 27% decrement in body weight gain (250 mg/kg/day). Liver enlargement (75 and 250 mg/kg/day), hepatocyte fat vacuolation (dose related) and centrilobular hypertrophy with increased expression of CYP2B1/2 and CYP3A at 250 mg/kg/day. Increased TSH and T_4 and thyroid follicular cell hypertrophy (250 mg/kg/day). Thyroid pigmentation (all doses). Adrenal cortical vacuolation (75 mg/kg/day and above). Increased pancreatic glucagon secreting cells (75 mg/kg/day and above). Increased alveolar macrophages (75 mg/kg/day and above).

Table 6: Principal Multiple Dose Toxicity Studies with Quetiapine

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Dog Beagle	oral tablets	4 weeks	3	0 25 50 100	Decreased motor activity, ataxia, somnolence, miosis, increased heart rate and hypothermia were observed for animals in all compound-treated groups. In general the incidence was dose-related and decreased with time. All effects reversed on withdrawal.
Dog Beagle	oral tablets	6 months dosing and 8 weeks withdrawal	3 or 4	0 25 50 100	Up to 8 weeks transient sedation and increased heart rate. Dose-related decreases in body weight gain. At 100 mg/kg/day 13-26% decrease in plasma cholesterol and prominent posterior Y sutures, swelling of lens fiber tips and 3/8 females with cataracts; 1 epileptiform seizure, 4/8 muscular twitching. 50 mg/kg/day was the no adverse-effect dose level.
Dog Beagle	Oral Tablets	12 months dosing and 8 weeks withdrawal	4z	0 10 25 50 100	Sedation, miosis, abnormal gait and muscular tremors occurred at doses of 25 mg/kg/day and above, mainly in the first 10 weeks. Cataracts in animals given 100 mg/kg/day. Histopathological lenticular changes in 5/8 dogs given 50 mg/kg/day. At 100 mg/kg/day 13/14 dogs showed histological lenticular alterations, consistent with the ophthalmological observations. Fine brown granules in the epithelial cells of the lacrimal glands at all doses.

Table 6: Principal Multiple Dose Toxicity Studies with Quetiapine

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Cynomolgus monkey	oral gavage	13 months	4	0, rising dose for 4 weeks with one week at each dose level then 43.5 for 52 weeks	Signs of sedation from week 2, duration and severity increased with dose. 43.5 mg/kg/day was considered to be the maximum tolerated dose. Abnormal staring behaviour in 2 animals. Plasma prolactin reduced. No compound-related histopathological changes. No effect on plasma cholesterol. No ophthalmological changes were observed.
Cynomolgus monkey	oral gavage	14 weeks	3	6, 12, 24, 36, 48, 60, 84, 108, 132,150, 180, 225, 285 and 350. Rising doses administered 3 doses/day. One week at each dose level	Sedation from 24 mg/kg/day, after which the duration and severity increased with dose, until at 225 mg/kg/day prostration occurred. Doses at 285 and 350 mg/kg/day caused reduction in body weight and food consumption, ataxia, increased incidence of prostration and one animal died at 350/mg/kg/day. Reductions in red blood cell parameters, plasma bilirubin, cholesterol (20-40% at 285 mg/kg) and ALP activity. No compound-related histopathological changes.

Table 6: Principal Multiple Dose Toxicity Studies with Quetiapine

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Cynomolgus monkey	oral gavage	56 weeks dosing 4 weeks withdrawal	4	0, rising dose for 4 weeks then 25, 100 and 225 mg/kg/day administered as 3 doses/day	Dose-related incidence and severity of behavioural changes. No abnormal signs on drug withdrawal. 40-60% reduction in plasma cholesterol at 225 mg/kg/day with delta-8-cholestanol present at 15% of cholesterol level at 100 and 225 mg/kg/day. No lens opacities. Minor lens changes at all doses with no lens pathology. Transient elevation of prolactin and mild mammary gland hyperplasia (in males) and T_3 levels reduced and mild thyroid follicular cell hypertrophy at 100 and 225 mg/kg/day. Red cell indices reduced and liver enlargement with hepatocyte hypertrophy and fat deposition at 225 mg/kg/day.

Table 7: Carcinogenicity (And Mouse Sighting) Studies With Quetiapine

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Mouse C57BL/ 10jfCD/1/Alpk	Oral in diet	90 days	25	0, 50, 100, 200, 300, 400	Reductions in body weight at 100 mg/kg or greater. Seminiferous tubular atrophy severity increased at 100 mg/kg and above. Centrilobular hepatocyte enlargement at 200 mg/kg and above. At 50 mg/kg the only effect was an increase in liver weight in females.
Mouse C57BL/ 10jfCD/1/Alpk	Oral in diet	90 days	15	0, 300-800, 400-1,100 (Rising dose maximal at 6 weeks)	Reduced body weight, liver weight increase and hepatocyte hypertrophy in both dose groups. Ovary weight decreased in high dose females and testicular weight decreased in low and high dose males. Low and high dose females had dose related decreases in number of corpora lutea. The parotid salivary gland had dose-related increased basophilia. Males had dose-related seminiferous tubular atrophy. Urinary bladder hyaline droplets and pigmentation in the epithelium in both groups.
Mouse C57BL/ 10jfCD/1/Alpk	Oral in diet	2 years	100, 50, 50, 50, 50	0, 20, 75, 250, 750 (Rising dose maximal at 6 weeks)	Thyroid follicular cell hypertrophy and pigmentation. Increased incidence of thyroid follicular cell benign adenomas (incidence of 0%, 0%, 0%, 8% and 58% in males only at 0, 20, 75, 250 and 750 mg/kg/day, respectively). No other increases in tumour incidence. Other non-neoplastic changes similar to sighting studies.

Table 7: Carcinogenicity (And Mouse Sighting) Studies With Quetiapine

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Rat/ Crl:(WI)BR	Oral by gavage	2 years	100 50 50 50 50	0 20 75 250	Increased incidence of mammary adenocarcinomas in all groups of females (incidence of 10%, 26%, 22% and 32% in females given 0, 20, 75 and 250 mg/kg/day respectively). Increased incidence of follicular adenoma of the thyroid gland in males, but not females, given 250 mg/kg/day (incidence of 6%, 6%, 0% and 32% in males given 0, 20, 75 and 250 mg/kg/day respectively). Significant reductions in subcutaneous fibromas, thyroid parafollicular cell adenomas, uterine stromal polyps and carcinoma of the oral cavity.

Table 8: Reproduction and Teratology Studies with Quetiapine

Species/Strain	Route	Study Duration	Number/ Group	Dose (mg/kg/day)	Salient Observations
Rat Alpk:APfSD Segment I Male fertility	Oral	males dosed for a total of 14 weeks	F_o generation: 1st pairing: 100 M, 200 F, 25 M, 50 F/Gp 2nd pairing: 25 M, 50 F/Gp (Groups I & IV only)	0, 25, 50, 150 males only dosed, to the end of the first pairing period	First pairing: Reduced weight gain and marked clinical signs at all quetiapine dose levels. Reduced fertility in males dosed 150 mg/kg/day (longer precoital with second female). Second pairing: Effects on reduced fertility reversed, no difference between control and quetiapine dosed animals.
Rat Alpk:APfSD Segment I Female fertility	Oral	9 months F_o generation: dosed to d14 prior to pairing up to d24 pp in animals assigned to litter	F_o generation: 264 M/132 F 66 F/Gp 33 M/Gp - not dosed F_1 generation: 239 F/120 M 50 F/Gp (49 Gp I) 25 M/Gp	0, 1, 10, 50 50 mg/kg/day dose reduced to 1 mg/kg/day from d17 gestation to d6 pp to avoid litter loss F_1 generation not dosed	Inhibition of oestrus cyclicity during dosing at 50 mg/kg/day, females became pseudopregnant or with protracted periods of dioestrus, increased precoital interval and reduced pregnancy rate. Slight reduction in body weight gain during pregnancy and lactation at 50 mg/kg/day. No effects on fertility or reproduction in the F_1 generation.
Rat Alpk:APfSD Segment II Teratology	Oral	21 days females dosed d6 to d15 gestation	F_o generation: 22 F 22 F 22 F 22 F		Reduced weight gain and adverse clinical signs at 50 and 200 mg/kg/day. No effects on fetal survival. Fetal weight reduced at 200 mg/kg/day. No major fetal abnormalities. Specific skeletal anomalies present associated with reduced fetal weight at 200 mg/kg/day.

Table 8: Reproduction and Teratology Studies with Quetiapine

Species/Strain	Route	Study Duration	Number/ Group	Dose (mg/kg/day)	Salient Observations
Rat Crj: Wistar Segment II Teratology	Oral	21 days females dosed from d6 to d15 gestation	F_o generation: 13 F/group	0, 25, 50, 200	Adverse clinical signs at all dose levels. No effect on reproductive function of the dams or development of fetuses, behaviour or reproductive function of the offspring at any dose level.
Rabbit Dutch Belted Segment II Teratology	Oral	28 days females dosed d6 to d18 gestation	F_o generation: 20 F 20 F 20 F 20 F	0 25 50 100	Reduced weight gain and adverse clinical signs at all doses. No effects on fetal survival. Fetal weight reduced at 100 mg/kg/day. No major fetal abnormalities. Specific skeletal anomalies present associated with reduced fetal weight at 100 mg/kg/day.
Rat/ Alpk:AP_fSD Segment III Peri- & Postnatal	Oral	44 days dosed d16 to d21 pp	F_o generation: 20 F 20 F 20 F 20 F	0 1 10 20	Reduced weight gain during first 2 weeks of lactation 20 mg/kg/day. No effects on survival or development of offspring.

M = Male, F = Female
d6 = day 6 gestation, day of sperm positive smear (rats)/day of mating rabbits) = day 0 gestation
d16 = day 16 gestation, day of mating = day 1 gestation
d17 = day 17 gestation, day of sperm positive smear = day 1 gestation
d6 pp = day 6 post partum, day of parturition = day 1 post partum
d8 pp = day 8 post partum, day of littering = day 1 post partum
d21 pp = day 21 post partum, day of littering = day 1 post partum
d24 pp = day 24 post partum, day of littering = day 1 post partum
(pp = post partum)

17. SUPPORTING PRODUCT MONOGRAPHS

1. PrSEROQUEL® Oral Use Immediate-Release Tablets, 25, 100, 200 and 300 mg, submission control 254368, Product Monograph, AstraZeneca Canada Inc. (Nov 29, 2021)

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]MINT-QUETIAPINE
quetiapine fumarate immediate-release tablets

Read this carefully before you start taking **MINT-QUETIAPINE** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **MINT-QUETIAPINE**.

Serious Warnings and Precautions

- MINT-QUETIAPINE belongs to a group of medicines called atypical antipsychotics. These medicines have been linked to a higher rate of death when used in elderly patients with dementia (loss of memory and other mental abilities).
- MINT-QUETIAPINE is not to be used if you are elderly and have dementia.

What MINT-QUETIAPINE is used for?
MINT-QUETIAPINE is used to treat symptoms of schizophrenia in adults. Not all people with this disorder have the same symptoms. Some of the most common symptoms of schizophrenia may include:
- hallucinations (seeing, feeling, hearing or smelling things that are not there)
- delusions (believing things that are not true)
- paranoia (not trusting others or feeling very suspicious)
- avoiding family members and friends and wanting to be alone
- feeling depressed, anxious or tense

MINT-QUETIAPINE is also used to treat adults who suffer from manic or depressive episodes in bipolar disorder. Bipolar disorder is a condition with symptoms such as:
- feeling invincible or an all powerful inflated self-esteem
- having racing thoughts, easily losing train of thought
- overreacting to what you see or hear
- misinterpreting events
- speeding-up your activities, talking very quickly, too loudly, or more than usual
- needing less sleep
- having poor judgment
- severe irritability
- feeling sad or hopeless
- loss of interest and enjoyment
- feeling tired

MINT-QUETIAPINE is not a cure for your condition, but it can help manage your symptoms and help you feel better.

How does MINT-QUETIAPINE work?
Antipsychotic medications affect the chemicals that allow communication between nerve cells (neurotransmitters). Illnesses that affect the brain may be due to certain chemicals (dopamine and serotonin) in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Exactly how MINT-QUETIAPINE works is unknown. However, it seems to adjust the balance of these chemicals.

What are the ingredients in MINT-QUETIAPINE?
Medicinal ingredients: quetiapine fumarate

Non-medicinal ingredients: dibasic calcium phosphate dihydrate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate, hypromellose, titanium dioxide, macrogol, iron oxide yellow (25 mg, 100 mg and 150 mg tablets), and iron oxide red (25 mg tablets).

MINT-QUETIAPINE comes in the following dosage forms:
Immediate-release tablets: 25 mg, 100 mg, 150 mg, 200 mg and 300 mg.

Do not use MINT-QUETIAPINE if:
- You are allergic to quetiapine fumarate or to any of the ingredients in MINT-QUETIAPINE (see list of Non-medicinal ingredients).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take MINT-QUETIAPINE. Talk about any health conditions or problems you may have, including if you:
- Have had an allergic reaction to any medicine that you have taken to treat your condition.
- Are pregnant, think you may be pregnant or plan to become pregnant.
- Are breast-feeding or are planning to breast-feed. You should not breast-feed while taking MINT-QUETIAPINE.
- Drink alcohol or use street drugs.
- Have a history of alcohol or drug abuse.
- Have low or high blood pressure.
- Have had a stroke or are at risk for stroke.
- Have or have a family history of:
    - heart problems
    - any problems with the way your heart beats
    - heart disease
- Have a history of seizures (fits).
- Have diabetes or a family history of diabetes as MINT-QUETIAPINE may increase your blood sugar levels.
- Have a history of liver or kidney problems.
- Know that you have or have had a low white blood cell count in the past.
- Exercise vigorously or work in hot or sunny places.
- Have risk factors for developing blood clots such as:
    - a family history of blood clots
    - being over the age of 65
    - smoking
    - being overweight
    - having a recent major surgery (such as hip or knee replacement)
    - not being able to move due to air travel or other reasons
    - taking oral birth control (“The Pill”)
- Suffer or have ever suffered from severe constipation, a blocked bowel or any other condition that affects your large bowel.
- Have or have had sleep apnea (a sleep disorder where your breathing is interrupted during sleep) or are taking medicines that slow down normal activity of the brain (“depressants”) or breathing.
- Have or have had a condition where your bladder does not empty or does not empty completely (urinary retention).
- Have narrow angle glaucoma or pressure inside your eyes.
- Are at risk for aspiration pneumonia.

Other warnings you should know about:

Self-harm: If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital right away. You may find it helpful to tell a relative or close friend that you are depressed or have other mental illnesses. Ask them to read this leaflet. You might ask them to tell you if they:

- Think your depression or mental illness is getting worse.
- Are worried about changes in your behaviour.

Effects on Newborns: In some cases, babies born to a mother taking MINT-QUETIAPINE during pregnancy have symptoms of withdrawal that are severe and require the newborn to be hospitalized. Sometimes, the symptoms may resolve on their own. Be ready to seek emergency medical help for your newborn if they:
- Have trouble breathing.
- Are overly sleepy.
- Have muscle stiffness, or floppy muscles (like a rag doll).
- Are shaking.
- Are having difficulty feeding.

Monitoring and Tests: Your doctor may do tests before you start treatment with MINT-QUETIAPINE and they may monitor you during treatment. These tests may include:
- Blood tests to monitor:
  - blood sugar
  - red and white blood cell count
  - amount of platelets
  - liver enzymes
  - lipid levels (a type of fatty substance in your body)
  - creatine phosphokinase levels (a substance in muscles)
  - prolactin levels (a hormone in your body)
- Body weight checks to monitor any weight gain.
- Eye examinations to monitor any lens changes in your eyes.

Dehydration and Overheating: It is important not to become too hot or dehydrated while you are taking MINT-QUETIAPINE.
- Do not exercise too much.
- In hot weather, stay inside in a cool place if possible.
- Stay out of the sun.
- Do not wear too much clothing or heavy clothing.
- Drink plenty of water.

Driving and Using Machines: MINT-QUETIAPINE may make you feel sleepy. Give yourself time after taking MINT-QUETIAPINE to see how you feel before driving a vehicle or using machinery.

Heart Problems: Cardiomyopathy (weakening of the heart muscle) and myocarditis (inflammation of the heart) have been reported in some patients. However, it is not known if MINT-QUETIAPINE treatment is related to these problems.

MINT-QUETIAPINE can cause serious side effects including:
- Neuroleptic Malignant Syndrome (NMS) a condition that affects the nervous system.
- Severe skin reactions that can be life-threatening such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).
- Tardive Dyskinesia (TD) and Extrapyramidal Symptoms (EPS), disorders that affect your movements.
- Pancreatitis (inflammation of the pancreas).

See the **Serious side effects and what to do about them** table below for more information on these and other serious side effects. Talk to a healthcare professional **right away** if you think you are experiencing any of these serious side effects.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with MINT-QUETIAPINE:
- MINT-QUETIAPINE can increase the effects of the alcohol.
- Medicines used to treat high blood pressure such as diltiazem, verapamil.
- Medicines used to treat seizures such as carbamazepine, phenytoin, divalproex.
- Medicines used to treat psychosis such as thioridazine.
- Medicines used to treat depression such as nefazodone.
- Medicines used to treat infections (antibiotics) such as erythromycin, clarithromycin.
- Medicines called "anticholinergics", which cause constipation or may affect your ability to empty your bladder.
- Ketoconazole, a drug used to treat fungal infections.
- Levodopa, a drug used to treat Parkinson's and other drugs called "dopamine agonists".
- Rifampin, a drug used to treat tuberculosis.
- Medicines that affect the way your heart beats, these include drugs known to cause electrolyte imbalance called "diuretics" ("water pills").
- Drugs called "protease inhibitors" used to treat Human Immunodeficiency Virus (HIV).

Effect on Urine Drug Screens: MINT-QUETIAPINE may cause positive results for methadone or certain drugs for depression called "tricyclic antidepressants" (TCAs), even if you are not taking these drugs. Tell your healthcare professional that you are taking MINT-QUETIAPINE so more specific tests can be conducted.

How to take MINT-QUETIAPINE:
- Even if you feel better, do **NOT** change your dose or stop taking MINT-QUETIAPINE without talking to your healthcare professional.
- MINT-QUETIAPINE can be taken with or without food.
- Try to take MINT-QUETIAPINE at the same time each day.

Usual dose:
Schizophrenia
The usual starting dose is 25 mg, twice daily. The recommended dose range is 25 to 400 mg, taken twice daily.

Bipolar Mania
The usual starting dose is 50 mg, twice daily. The recommended dose range is 50 to 400 mg, taken twice daily.

Bipolar Depression
The usual dosing schedule is 50 mg on day 1, 100 mg on day 2, 200 mg on day 3, and 300 mg on day 4 and onwards taken once daily. Your doctor may increase the dose to 400 mg on day 5 and up to 600 mg per day from day 8 onwards depending on your response and tolerability. The maximum dose is 600 mg per day.

It takes time to feel better and you should expect some symptoms to improve slowly over the first few weeks of treatment. Do not stop taking MINT-QUETIAPINE, or change the times of day you take MINT-QUETIAPINE, without talking to your doctor first.

If you stop taking MINT-QUETIAPINE abruptly you may experience withdrawal symptoms such as insomnia (not being able to sleep), nausea, and vomiting. Keep your doctor well informed of how you are feeling, both good and bad. By doing this, you and your doctor will be able to make sure that you get the best dose of MINT-QUETIAPINE for you.

Overdose:

If you think you, or a person you are caring for, have taken too much MINT-QUETIAPINE, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose by only a few hours, take it as soon as possible. If most of the day has passed since your missed dose, skip that dose and wait until your next scheduled dose. Never take two doses at once.

What are possible side effects from using MINT-QUETIAPINE?

These are not all the possible side effects you may have when taking MINT-QUETIAPINE. If you experience any side effects not listed here, tell your healthcare professional.

- Light-headedness or feeling faint
- Dizziness or drowsiness
- Falls
- Headache
- Fever and flu-like symptoms
- Sore throat
- Nausea or vomiting
- Indigestion
- Upset stomach or stomach pain
- Constipation
- Diarrhea
- Irritability
- Shortness of breath
- Slow or fast heart rate
- Feeling weak
- Swelling of arms and legs
- Blurred vision
- Dry mouth
- Difficulty swallowing
- Feeling more hungry
- Weight gain
- Trouble sleeping or falling asleep
- Abnormal dreams and nightmares
- Problems with speech or language

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Abnormal muscle movements, including difficulty starting muscle movements, shaking, restlessness or muscle stiffness without pain.		✓	
COMMON			
Hyperglycemia (high blood sugar): increased thirst, frequent urination, excessive hunger,		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
headache, blurred vision and fatigue.			
Hypotension (low blood pressure): dizziness, fainting, light-headedness, blurred vision, nausea, vomiting, fatigue (may occur when you go from lying or sitting to standing up).		✓	
New or worsening constipation.		✓	
UNCOMMON			
Confusion: impaired orientation, reduced attention, impaired memory, abnormal thought process.		✓	
Restless Legs Syndrome: unpleasant sensations in the legs.		✓	
Seizure (fits)**:** loss of consciousness with uncontrollable shaking.			✓
Tardive Dyskinesia: muscle twitching or unusual/abnormal movement of your face or tongue or other parts of your body.		✓	
Urinary Retention: not being able to pass urine.			✓
RARE			
Agranulocytosis (decreased white blood cell counts)**:** infections, fatigue, fever, aches, pains and flu-like symptoms.		✓	
Blood clots: swelling, pain and redness in an arm or leg that can be warm to touch. You may develop sudden chest pain, difficulty breathing and heart palpitations.		✓	
Hypothermia (low body temperature)**:** shivering, slurred speech or mumbling, slow, shallow breathing, weak pulse, very low energy, confusion or memory loss.		✓	
Intestinal blockage or obstruction (blockage that stops or impairs passage of contents of intestines)**:** cramping pain in abdomen that may begin suddenly, bloating, loss of appetite, pain that comes and goes but will then last, nausea and vomiting, constipation or diarrhea.		✓	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Liver Disorder: yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, loss of appetite.		✓	
Neuroleptic Malignant Syndrome (NMS)**:** severe muscle stiffness or inflexibility with high fever, rapid or irregular heartbeat, sweating, state of confusion or reduced consciousness.			✓
Pancreatitis (inflammation of the pancreas)**:** upper abdominal pain, fever, rapid heart beat, nausea, vomiting, tenderness when touching the abdomen.		✓	
Priapism: Long-lasting (greater than 4 hours in duration) and painful erection of the penis.			✓
Somnambulism (sleep-walking)**:** getting out of bed while not fully awake and doing activities like walking, talking or eating that you do not remember doing the day after.		✓	
VERY RARE			
Allergic Reaction: difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			✓
Rhabdomyolysis (breakdown of damaged muscle)**:** unexplained muscle pain, muscle tenderness, muscle weakness, red-brown (tea-coloured) urine.		✓	
Sleep Apnea: stop breathing for short periods during your normal nightly sleep.			✓
NOT KNOWN			
Inflammation of blood vessels (cutaneous vasculitis)**:** skin rash with small red or purple bumps.		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Severe skin reactions: fever, severe rash, swollen lymph glands, flu-like feeling, blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body, yellow skin or eyes, shortness of breath, dry cough, chest pain or discomfort, feeling thirsty, urinating less often, less urine.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
- Store MINT-QUETIAPINE at room temperature (between 15°C - 30°C).
- The expiry date of this medicine is printed on the package label. Do not use the medicine after this date.
- If your doctor tells you to stop taking MINT-QUETIAPINE or you find that the tablets have passed their expiry date, please return any leftover medicine to your pharmacist.

Keep out of reach and sight of children.

If you want more information about MINT-QUETIAPINE:
- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.mintpharmaceuticals.com, or by calling 1-877-398-9696.

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