PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr] NB-QUETIAPINE XR

Quetiapine fumarate extended-release tablets

Extended-Release Tablets, 50 mg, 150 mg, 200 mg, 300 mg and 400 mg quetiapine (as quetiapine fumarate), Oral Use

Manufacturer's Standard

Antipsychotic / Antidepressant Agent

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RECENT MAJOR LABEL CHANGES

N/A

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

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1 PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Schizophrenia

NB-Quetiapine XR (quetiapine fumarate extended-release) is indicated for:

- Management of the manifestations of schizophrenia.

Bipolar Disorder

NB-Quetiapine XR 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.

Major Depressive Disorder

NB-Quetiapine XR is indicated for:

- Symptomatic relief of major depressive disorder (MDD) when currently available approved antidepressant drugs have failed either due to lack of efficacy and/or lack of tolerability.

While there is no evidence that the efficacy of NB-Quetiapine XR is superior to other antidepressants, it provides a treatment option for patients who have failed on previous antidepressant treatments.

Clinicians must take into account the safety concerns associated with antipsychotic drugs, a class of drugs to which NB-Quetiapine XR belongs. Safety concerns of this class include: weight gain; hyperlipidemia; hyperglycemia; Tardive Dyskinesia; and Neuroleptic Malignant Syndrome (see 7 WARNINGS AND PRECAUTIONS). NB-Quetiapine XR should only be prescribed in patients with MDD by clinicians who are aware of the importance and are experienced in the early detection and management of the above-mentioned safety issues associated with this class.

Long-term safety of quetiapine fumarate extended-release in MDD has not been systematically evaluated. Thus, the physician who elects to use NB-Quetiapine XR in the treatment of MDD should use NB-Quetiapine XR for the shortest time that is clinically indicated. When lengthier treatment is indicated, the physician must periodically re-evaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks (see 14 CLINICAL TRIALS).

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of quetiapine fumarate extended-release in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use. (see 7 WARNINGS AND PRECAUTIONS, Special Populations).

Geriatrics (> 65 years of age): NB-Quetiapine XR is not indicated in elderly patients with dementia. (See 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS, Special Populations).

NB-Quetiapine XR 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.

ONS 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 WARNINGS AND PRECAUTIONS, Geriatrics - Use in Geriatric Patients with Dementia).

For considerations in special populations see section 4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment – Dosing Considerations in Special Populations.

e Adjustment

Schizophrenia

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

	Day 1	Day 2	After Day 2
Once daily dosing	300 mg	600 mg	Up to 800 mg

The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. In a controlled clinical trial, the treatment effect size of 600 mg and 800 mg doses of quetiapine fumarate extended release

was greater than that of the 400 mg dose (see 14 CLINICAL TRIALS).

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 extended-release 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	Day 2	After Day 2
Once daily dosing	300 mg	600 mg	Up to 800 mg

The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient.

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	Day 2	Day 3	Day 4 and thereafter
Once daily dosing	50 mg	100 mg	200 mg	300 mg

The usual target dose is 300 mg/day. The dose may be further increased depending on the response and tolerability of the patient. The maximum dose is 600 mg/day.

In quetiapine immediate-release formulation clinical trials antidepressant efficacy was demonstrated with quetiapine immediate-release formulation at both 300 mg/day and 600 mg/day, however no additional benefit was seen in the 600 mg group during short-term treatment.

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

Major Depressive Disorder

NB-Quetiapine XR is indicated for the symptomatic relief of major depressive disorder (MDD) when currently available approved antidepressant drugs have failed either due to lack of efficacy and/or lack of tolerability. While there is no evidence that the efficacy of NB-Quetiapine XR is superior to other antidepressants, it provides a treatment option for patients

who have failed on previous antidepressant treatments.

Clinicians must take into account the safety concerns associated with antipsychotic drugs, a class of drugs to which quetiapine fumarate extended-release belongs. Safety concerns of this class include: weight gain; hyperlipidemia; hyperglycemia; Tardive Dyskinesia; and Neuroleptic Malignant Syndrome (see 7 WARNINGS AND PRECAUTIONS). NB-Quetiapine XR should only be prescribed in patients with MDD by clinicians who are aware of the importance and are experienced in the early detection and management of the above-mentioned safety issues associated with this class.

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

	Day 1	Day 2	Day 3
Once daily dosing	50 mg	50 mg	150 mg

The usual target dose is 150 mg. Some patients may respond to doses as low as 50 mg/day and where clinically indicated dose may be increased to 300 mg/day after Day 4. In clinical trials, doses between 50 - 300 mg/day were shown to be efficacious, however, the incidence of certain adverse events increased with dose (see 8 ADVERSE REACTIONS, and 14 CLINICAL TRIALS).

In MDD, the safety of doses above 300 mg/day has not been evaluated.

Some of the safety concerns associated with NB-Quetiapine XR and this class of agents (i.e., antipsychotics), may be dose-related (see 7 WARNINGS AND PRECAUTIONS, and 8 ADVERSE REACTIONS). The NB-Quetiapine XR dose should thus be periodically reassessed to achieve and maintain the lowest effective dose. Furthermore, as the long-term safety of quetiapine fumarate extended-release in MDD has not been systematically evaluated, the physician who elects to use NB-Quetiapine XR in the treatment of MDD should use NB-Quetiapine XR for the shortest time that is clinically indicated. When long-term treatment is believed to be indicated, the physician must periodically re-evaluate the long-term usefulness of the drug for the individual patient keeping in mind the long-term risks.

Switching patients from NB-Quetiapine tablets to NB-Quetiapine XR tablets
For more convenient dosing, patients who are currently being treated with divided doses of NB-Quetiapine (quetiapine immediate release formulation) may be switched to NB-Quetiapine XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Switching patients from other antidepressants
For many antidepressants a gradual taper is recommended prior to complete discontinuation of the drug (physicians should refer to the approved Product Monograph of the specific

antidepressant). There are no systematically collected data to address switching patients from other antidepressants to quetiapine fumarate extended-release. Generally there should be no need for a wash-out period between stopping an antidepressant and starting NB-Quetiapine XR. The physician may elect to initiate NB-Quetiapine XR treatment while tapering the antidepressant, however patients may experience additive side effects during the overlap period.

Switching patients from other antipsychotics

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

The following cross-titration schedule has been used in clinical trials with schizophrenia:

	Day 1	**Day 2**	**Day 3**
Quetiapine fumarate extended-release	300 mg	600 mg	Up to 800 mg
% Reduction of ongoing antipsychotic treatment	75%	50%	25%

Dosing Considerations in Special Populations

Pediatric Use

Health Canada has not authorized an indication for pediatric use, as safety and efficacy of quetiapine fumarate extended-release in children under the age of 18 years have not been established (See 7 WARNINGS AND PRECAUTIONS, Special Populations)

Geriatric Use

As with other antipsychotics, NB-Quetiapine XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of NB-Quetiapine XR may need to be slower, and the daily therapeutic target dose lower, than that used in younger patients. In clinical trials, 68 patients, 65 years of age or over, were treated with quetiapine fumarate extended-release (see 7 WARNINGS AND PRECAUTIONS, Special Populations). Given the limited experience with quetiapine fumarate extended-release in the elderly, and the higher incidence of concomitant illness and concomitant medication in this population, NB-Quetiapine XR should be used with caution. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly subjects when compared to younger patients. Elderly patients should be started on the lowest available dose (i.e., 50 mg/day) of NB-Quetiapine XR. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the

clinical response and tolerance of the individual patient.

In elderly patients with MDD, initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, and 150 mg on Day 8 (see 14 CLINICAL TRIALS).

Hepatic Impairment
Quetiapine is extensively metabolized by the liver (see 10 CLINCIAL PHARMACOLOGY, Special Populations and Conditions). Therefore, NB-Quetiapine XR 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 the lowest available dose (i.e., 50 mg/day) of NB-Quetiapine XR. The dose should be increased daily in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerance in the individual patient. No pharmacokinetic data are available for quetiapine in patients with moderate to severe hepatic impairment. However, should clinical judgement deem treatment with NB-Quetiapine XR necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic and 10 CLINICAL PHARMACOLOGY, 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

NB-Quetiapine XR is for oral use only.
NB-Quetiapine XR tablets should be swallowed whole and not split, chewed, or crushed.
NB-Quetiapine XR should be administered once daily, generally in the evening.
NB-Quetiapine XR can be administered with or without food.

4.5 Missed Dose

NB-Quetiapine XR should be taken at the same time each day. If a previous day's dose has been missed, administration should be resumed the next day at the normal administration time.

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 immediate-release formulation overdose. The lowest reported dose associated with coma has been in a patient who took 5000 mg and had a full recovery within 3 days. The lowest reported dose associated with a death was in a patient who took 6000 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, Cardiovascular, Hypotension and Syncope).

NB-Quetiapine XR overdose may lead to gastric bezoar formation and an appropriate diagnostic imaging is recommended to further guide patient management. Routine gastric lavage may not be effective in the removal of the bezoar due to gum like sticky consistency of the mass. Endoscopic pharmacobezoar removal has been performed successfully in many cases.

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.

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

POSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral Use	Extended-Release Tablet 50 mg, 150 mg, 200 mg, 300 mg and 400 mg	Colloidal silicon dioxide, hydrogenated vegetable oil, lactitol, lactose monohydrate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, red iron oxide (50 mg tablets only), succinic acid, talc, titanium dioxide and yellow iron oxide (50 mg, 200 mg and 300 mg tablets only).

NB-Quetiapine XR (quetiapine fumarate extended-release) is available as film-coated tablets containing quetiapine fumarate equivalent to 50 mg, 150 mg, 200 mg, 300 mg or 400 mg of quetiapine free base as follows:

50 mg quetiapine tablets are peach coloured, capsule-shaped, biconvex, engraved with ‘Q50’on one side and plain on the other, available in high-density polyethylene (HDPE) bottles of 100 tablets.

150 mg quetiapine tablets are white, capsule-shaped, biconvex, engraved with ‘Q150’ on one side and plain on the other, available in HDPE bottles of 100 tablets.

200 mg quetiapine tablets are yellow, capsule-shaped, biconvex, engraved with ‘Q200’ on one side and plain on the other, available in HDPE bottles of 100 tablets.

300 mg quetiapine tablets are pale yellow, capsule-shaped, biconvex, engraved with ‘Q300’ on one side and plain on the other, available in HDPE bottles of 100 tablets.

400 mg quetiapine tablets are white, capsule-shaped, biconvex, engraved with ‘Q400’ on one side and plain on the other, available in HDPE bottles of 100 tablets.

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents (including quetiapine fumarate extended-release). Appropriate care is advised when prescribing quetiapine fumarate extended-release 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 ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Other Adverse Events, Pyrexia.

Dependence / Tolerance
There have been reports of quetiapine misuse, abuse, tolerance, and/or physical dependence. These cases include adult and adolescent patients using NB-Quetiapine XR alone or with other substances of abuse. Caution is needed when prescribing NB-Quetiapine XR to patients with a history of alcohol or drug abuse. Patients should be observed closely for signs of NB-Quetiapine XR 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 (see 8 ADVERSE REACTIONS).

Carcinogenesis and Mutagenesis
For animal data, see 16 NON-CLINICAL TOXICOLOGY.

Cardiovascular
Hypotension and Syncope
As with other drugs that have high α1 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).

In placebo-controlled quetiapine fumarate extended-release tablet trials, there was little difference in the adverse reaction reporting rate of syncope in patients treated with quetiapine fumarate extended-release (0.5%, 11/2388) compared to patients on placebo (0.3%, 4/1267).

Syncope was reported in 1% (35/4083) of patients treated with quetiapine immediate-release formulation compared with 0.3% (3/1006) on placebo and 0.4% (2/527) on active control drugs.

NB-Quetiapine XR 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 schizophrenia clinical trials, quetiapine fumarate extended-release tablets-treated patients had increases from baseline in mean cholesterol and triglycerides of 4% and 14%, respectively, compared to decreases from baseline in mean cholesterol and triglycerides of 2% and 6% for placebo-treated patients. In a 3-week bipolar mania clinical trial, quetiapine fumarate extended-release tablets-treated patients had increases from baseline in mean cholesterol and triglycerides of 2% and 20%, respectively, compared to decreases in mean cholesterol and triglycerides of 2% and 5% for placebo-treated patients. In a bipolar depression clinical trial,

quetiapine fumarate extended-release tablets-treated patients had decreases from baseline in mean cholesterol and increases from baseline in mean triglycerides of 2% and 11%, respectively, compared to decreases in mean cholesterol and triglycerides of 3% and 2% for placebo-treated patients. In
6-week MDD monotherapy clinical trials, quetiapine fumarate extended-release treated patients had increases from baseline in mean triglycerides of 8%, compared to a mean decrease of 1% for placebo-treated patients. In the same trials, both quetiapine fumarate extended-release tablets- and placebo-treated patients had decreases from baseline in mean cholesterol of 1% and 3%, respectively. In a longer-term randomized withdrawal MDD trial (see 14 CLINICAL TRIALS), patients who completed at least 158 days of quetiapine fumarate extended-release treatment (n = 196), showed mean increases from baseline in triglycerides of approximately 5% and mean decreases from baseline in cholesterol of approximately 4%.

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 (≥ 0.01% - < 0.1%) during the use of quetiapine in post-marketing experience, sometimes in patients with no reported history of hyperglycemia (see 8 ADVERSE REACTIONS, Post-Market Adverse Reactions).

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. Occasional reports of diabetes, have also been observed in clinical trials with quetiapine (see 8 ADVERSE REACTIONS, 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 are 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 hyperglycaemia-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 6-week placebo-controlled schizophrenia clinical trials, for patients treated with quetiapine fumarate extended-release mean weight gain was 1.77 kg (n = 951) compared to 2.19 kg (n = 414) in patients treated with quetiapine fumarate immediate-release tablets. For patients treated with placebo the mean weight gain was 0.26 kg (n = 319). In a 3-week placebo-controlled bipolar mania clinical trial, for patients treated with quetiapine fumarate extended-release mean weight gain was 1.3 kg (n = 151) compared to 0.1 kg (n = 160) in patients treated with placebo. In an 8-week placebo-controlled bipolar depression clinical trial, for patients treated with quetiapine fumarate extended-release mean weight gain was 1.3 kg (n = 137) compared to -0.2 kg (n = 140) in patients treated with placebo. In 6-week placebo-controlled MDD acute monotherapy clinical trials, for patients treated with quetiapine fumarate extended-release mean weight gain was 0.87 kg (n = 1149) compared to 0.31 kg (n = 648) in patients treated with placebo. In a longer-term randomized withdrawal MDD trial (see 14 CLINICAL TRIALS), patients who completed at least 158 days of quetiapine fumarate extended-release treatment (n = 196), mean weight gain for patients in quetiapine fumarate extended-release 50, 150 and 300 mg/day groups was 1.0 kg, 2.5 kg, and 3.0 kg respectively. In these same patients the percentage of patients experiencing a weight increase of ≥7% by 158 days in quetiapine fumarate extended-release 50, 150, and 300 mg/day groups was 13%, 24%, and 33% respectively.

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 immediate-release formulation across the recommended dose range, and placebo.

Hypothyroidism

In quetiapine fumarate extended-release clinical trials, 0.2% (4/1755) of patients on quetiapine fumarate extended-release compared to 0% (0/796) on placebo experienced decreased free thyroxine and 2.7% (46/1716) on quetiapine fumarate extended-release compared to 1.4% (11/785) on placebo experienced increased TSH; however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. In schizophrenia trials, no patients had events of hypothyroidism.

In clinical trials, on average quetiapine immediate-release formulation was associated with about a 20% mean reduction in thyroid thyroxine levels (both total and free). Forty-two percent of quetiapine immediate-release formulation-treated patients showed at least a 30% reduction in total T4 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 immediate-release formulation. These reductions were maintained without adaptation or progression during longer term treatment. Decreases in T4 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 immediate-release formulation 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 WARNINGS AND PRECAUTIONS, 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 ADVERSE REACTIONS, 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 extended-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 extended-release. It is recommended that patients have their complete blood count (CBC) tested prior to starting NB-Quetiapine XR and then periodically throughout treatment.

Severe neutropenia (<0.5 x 109/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 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions – Other Adverse Events 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 NB-Quetiapine XR 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 109/L) should discontinue NB-Quetiapine XR and have their WBC followed until recovery (see 8 ADVERSE REACTIONS, Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data and Post-Market Adverse Reactions).

Venous Thromboembolism

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

Hepatic/Biliary/Pancreatic

Hepatic Impairment

Decreased clearance of quetiapine immediate-release formulation was observed in patients with mild hepatic impairment (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions). No pharmacokinetic data are available for quetiapine fumarate extended-release in patients with moderate or severe hepatic impairment. However, should clinical judgement deem treatment with quetiapine necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see 10 CLINICAL PHARMACOLOGY - 10.3 Pharmacokinetics, Special Populations and Conditions and 4 DOSAGE AND ADMINISTRATION).

Transaminase Elevations

Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) associated with quetiapine fumarate extended-release have been reported. The proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of placebo-controlled trials were approximately 1% for both quetiapine fumarate extended-release and placebo.

During premarketing clinical trials, therapy with quetiapine immediate-release formulation was associated with elevation of hepatic transaminases, primarily ALT. Within a clinical trial database of 1892 quetiapine immediate-release formulation-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 immediate-release formulation-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 immediate-release formulation therapy. Of the 101 quetiapine immediate-release formulation-treated patients whose enzyme levels increased to > 120 IU/L, 40 discontinued treatment while their ALT values were still raised. In 114 quetiapine

immediate-release formulation-treated patients whose baseline ALT was > 90 IU/L, only 1 experienced an elevation to >400 IU/L.

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 postmarketing period. There have been rare reports of hepatitis in clinical studies. Rare postmarketing 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 ADVERSE REACTIONS, 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 (NMS)

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 and major depressive disorder, 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 NB-Quetiapine XR 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 clinical trials with quetiapine, there was no difference in the incidence of seizures in patients treated with quetiapine (0.04%, 1/2388) or placebo (0.2%, 3/1267). 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 extended-release discontinuation or dose reduction. NB-Quetiapine XR 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, NB-Quetiapine XR dose reduction or gradual discontinuation and alternative therapeutic options should be considered (see 8 ADVERSE REACTIONS, 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 extended-release-treated patients with or without prior history. Some patients experiencing severe urinary retention were hospitalized and required catheterization. Quetiapine fumarate extended-release 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, NB-Quetiapine XR 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, Gastrointestinal - 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). NB-Quetiapine XR 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 NB-Quetiapine XR and alternative therapy should be considered (see 8 ADVERSE REACTIONS, 9 DRUG INTERACTIONS, 5 OVERDOSAGE, 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 immediate-release formulation treatment, but a causal relationship to quetiapine immediate-release formulation use has not been established. The possibility of lenticular changes during long-term use of quetiapine fumarate extended-release in man, thus cannot be excluded at this time. Eye examinations (e.g., slit lamp exam) prior to or shortly after initiation of treatment with NB-Quetiapine XR and at 6 month intervals thereafter, are recommended. If clinically significant lens changes associated with NB-Quetiapine XR use are observed, discontinuation of NB-Quetiapine XR 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 and MDD, 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 a bipolar mania clinical trial with quetiapine fumarate extended-release tablets, the incidence of treatment emergent suicidal ideation or suicidal behaviour, as measured by the Columbia Analysis of Suicidal Behaviour, was 1.3% for quetiapine fumarate extended-release treated patients and 3.8% for placebo-treated patients.

In a bipolar depression clinical trial with quetiapine fumarate extended-release tablets, the incidence of treatment emergent suicidal ideation or suicidal behaviour, as measured by the Columbia Analysis of Suicidal Behaviour, was 0.7% for quetiapine fumarate extended-release treated patients and 1.4% for placebo-treated patients.

In MDD acute clinical trials, the incidence of treatment emergent suicidal ideation or suicide attempt was 0.7% in quetiapine fumarate extended-release treated patients and 0.7% in placebo-treated patients. In a longer-term randomized withdrawal study in patients with MDD, the incidence during randomized treatment was 0.3% for quetiapine fumarate extended-release and 0.5% for placebo.

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 extended-release tablets in patients with renal impairment, except in a low (subclinical) single dose study with quetiapine immediate-release formulation (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics – Special Populations and Conditions). NB-Quetiapine XR 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.

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. Therefore, quetiapine should only be used during pregnancy if the expected benefits justify the potential risks.

NB-Quetiapine XR should not be used during pregnancy unless the expected benefits to the mother markedly outweigh the potential risks to the fetus.

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.

Pediatrics (< 18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of quetiapine fumarate extended-release in pediatric patients has 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 ADVERSE REACTIONS, 8.3.1 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 quetiapine fumarate extended-release 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.

Geriatrics (≥ 65 years of age): The number of patients 65 years of age or over exposed to quetiapine during clinical trials was limited (n = 68). 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 patients (see 4 DOSAGE AND ADMINISTRATION).

In a clinical trial that evaluated non-demented elderly patients (aged 66 to 89 years) with MDD, the tolerability of quetiapine fumarate extended-release once daily was comparable to that seen in adults (aged 18-65 years) other than the incidence of extrapyramidal symptoms. See 7 WARNINGS AND PRECAUTIONS, Neurologic, Tardive Dyskinesia (TD) and Extrapyramidal Symptoms (EPS); 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS.

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 extended-release, showed increased mortality compared to the 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.

NB-Quetiapine XR 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. NB-Quetiapine XR is not indicated in patients with dementia.

Vascular disease

NB-Quetiapine XR 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. NB-Quetiapine XR 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).

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.

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 of 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:
In short-term, placebo-controlled schizophrenia trials, there was no difference in the incidence of adverse events associated with discontinuation of quetiapine fumarate extended release or placebo. Overall, 6.4% of quetiapine fumarate extended-release -treated patients discontinued treatment due to adverse events compared to 7.5% of placebo-treated patients.

Bipolar Disorder:
Bipolar Mania: In a 3-week placebo-controlled bipolar mania trial, 4.6% of patients on quetiapine fumarate extended-release discontinued due to adverse events compared to 8.1% on placebo.

Bipolar Depression: In an 8-week placebo-controlled bipolar depression trial, 13.1% of patients on quetiapine fumarate extended-release discontinued due to adverse events compared to 3.6% on placebo. Sedation (6.6%) and somnolence (3.6%) were the most common adverse events leading to discontinuation in the quetiapine fumarate extended-release treatment group.

Major Depressive Disorder:
In placebo-controlled monotherapy MDD trials, 14.3% of patients on quetiapine fumarate extended-release discontinued due to adverse events compared to 4.5% on placebo. In a placebo-controlled monotherapy trial in elderly patients with MDD, 9.6% of patients on quetiapine fumarate extended-release discontinued due to adverse events compared to 4.1% on placebo.

Commonly Observed Adverse Events in Short-Term Placebo-Controlled Clinical Trials
Schizophrenia:
During acute therapy with quetiapine fumarate extended-release, the most commonly observed adverse events associated with the use of quetiapine fumarate extended-release (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo) were sedation, dry mouth, somnolence, and dizziness.

Bipolar Disorder:
Bipolar Mania: During acute therapy with quetiapine fumarate extended-release, the most commonly observed adverse events associated with the use of quetiapine fumarate extended-release (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo) were sedation, dry mouth, somnolence, constipation, dizziness, weight gain and

dysarthria.

Bipolar Depression: During acute therapy with quetiapine fumarate extended-release, the most commonly observed adverse events associated with the use of quetiapine fumarate extended-release (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo) were dry mouth, somnolence, sedation, increased appetite, weight gain and dyspepsia.

Major Depressive Disorder:
The most commonly observed adverse events associated with the use of quetiapine fumarate extended-release (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo) during acute monotherapy with quetiapine fumarate extended-release were dry mouth, sedation, somnolence, dizziness and fatigue.

Incidence of Adverse Events in Placebo-Controlled Clinical Trials
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 extended-release (doses ranging from 300 to 800 mg/day) where the incidence in patients treated with quetiapine fumarate extended-release was greater than the incidence in placebo-treated patients.

Table 1 Adverse Events Reported for at Least 1% of Quetiapine Fumarate Extended-Release -Treated Subjects (Doses Ranging from 300 to 800 mg/day) and for a Higher Percentage of Quetiapine Fumarate Extended-Release **-Treated Subjects than Subjects Who Received Placebo in Short-Term, Placebo-Controlled Schizophrenia Phase III Trials**

Body System and MedDRA Term[a]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 951)	Placebo (n = 319)
Whole body		
Fatigue	3	2
Anxiety	2	1
Irritability	1	0
Pyrexia	1	0
Nervous system		
Sedation	13	7
Somnolence	12	4
Dizziness	10	4
Tremor	2	1
Restlessness	2	1
Gastrointestinal system		
Dry mouth	12	1

Body System and MedDRA Term[a]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 951)	Placebo (n = 319)
Constipation	6	5
Dyspepsia	5	2
Cardiovascular system		
Orthostatic hypotension	7	5
Hypotension	3	1
Tachycardia	3	1
Heart rate increased	4	1
Metabolic and nutritional disorders		
Increased appetite	2	0
Special senses		
Vision blurred	2	1

* Events for which quetiapine fumarate extended-release incidence was equal to or less than placebo are not listed in the table, but included the following: headache, insomnia, and nausea.

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

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (3 weeks) of bipolar mania in ≥ 1% of patients treated with quetiapine fumarate extended-release (300-800 mg/day) where the incidence in patients treated with quetiapine fumarate extended-release was greater than the incidence in placebo-treated patients.

Table 2 Adverse Events Reported for at Least 1% of Quetiapine Fumarate Extended-Release -Treated Subjects (Doses Ranging from 300 to 800 mg/day) and for a Higher Percentage of Quetiapine Fumarate Extended-Release -Treated Subjects than Subjects Who Received Placebo in a Short-Term (3-Week), Placebo-Controlled Bipolar Mania Phase III Trial

Body System and MedDRA Term[a]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 151)	Placebo (n = 160)
General disorders and administration site conditions		
Fatigue	7	4
Contusion	1	0
Pain	1	0
Nervous system disorders		
Sedation	34	8

Body System and MedDRA Term[a]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 151)	Placebo (n = 160)
Somnolence	17	4
Dizziness	10	4
Dysarthria	5	0
Lethargy	2	1
Sluggishness	2	1
Dizziness postural	1	0
Gastrointestinal disorders		
Dry mouth	34	7
Constipation	10	3
Dyspepsia	7	4
Toothache	3	1
Cardiovascular disorders		
Heart rate increased	3	0
Orthostatic hypotension	3	0
Tachycardia	2	1
Metabolic and nutritional disorders		
Weight increased	7	1
Increased appetite	4	2
Musculoskeletal and connective tissue disorders		
Back pain	3	2
Arthralgia	1	0
Psychiatric disorders		
Abnormal dreams	3	0
Bipolar I disorder	1	0
Respiratory disorders		
Nasal congestion	5	1
Dry throat	1	0
Special senses		
Vision blurred	2	1

* Events for which quetiapine fumarate extended-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.

Table 3 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 extended-release (300 mg/day) where the incidence in patients treated with quetiapine fumarate extended-release was greater than the incidence in placebo-treated patients.

Table 3 Adverse Events Reported for at Least 1% of Quetiapine Fumarate Extended-Release -Treated Subjects (Dose of 300 mg/day) and for a Higher Percentage of Quetiapine Fumarate Extended-Release -Treated Subjects than Subjects Who Received Placebo in a Short-Term (8-Week), Placebo-Controlled Bipolar Depression Phase III Trial

Body System and MedDRA Term[a]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 137)	Placebo (n = 140)
General disorders		
Fatigue	6	2
Irritability	4	3
Anxiety	2	1
Nervous system disorders		
Somnolence	29	6
Sedation	23	7
Dizziness	13	11
Paresthesia	3	2
Dysarthria	2	0
Disturbance in attention	2	1
Hypersomnia	1	0
Akathisia	1	0
Mental impairment	1	0
Gastrointestinal disorders		
Dry mouth	37	7
Constipation	8	6
Dyspepsia	7	1
Toothache	3	0
Cardiovascular disorders		
Heart rate increased	1	0
Infection and Infestations		
Gastroenteritis viral	4	1
Urinary tract infection	2	0
Metabolic and nutritional disorders		
Increased appetite	12	6
Weight increased	7	1
Decreased appetite	2	1

Body System and MedDRA Term[a]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 137)	Placebo (n = 140)
Musculoskeletal and connective tissue disorders		
Arthralgia	4	1
Back pain	3	1
Muscle spasm	3	1
Neck pain	1	0
Psychiatric disorders		
Abnormal dreams	3	0
Confusional state	1	0
Disorientation	1	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2	1

* Events for which quetiapine fumarate extended-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.

Table 4 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute monotherapy (up to 8 weeks) of MDD in ≥ 1% of patients treated with quetiapine fumarate extended-release (50 - 300 mg/day) where the incidence in patients treated with quetiapine fumarate extended-release was greater than the incidence in placebo-treated patients.

Table 4 Adverse Events Reported for at Least 1% of Quetiapine Fumarate Extended-Release-Treated Subjects (Doses Ranging From 50 to 300 mg/day) and for a Higher Percentage of Quetiapine Fumarate Extended-Release-Treated Subjects Than Subjects Who Received Placebo in Short-Term, Placebo-Controlled MDD Monotherapy Phase III Trials

Body System and MedDRA Term[a,b]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 1149)	Placebo (n = 648)
General disorders and administration site conditions		
Fatigue	7	2
Irritability	4	3
Nervous system disorders		

Body System and MedDRA Term[a,b]	Percentage of Subjects With Adverse Events*	
	Quetiapine Fumarate Extended-Release (n = 1149)	Placebo (n = 648)
Sedation	28	4
Somnolence	24	7
Dizziness	14	8
Disturbance in attention	2	< 1
Hypersomnia	2	< 1
Lethargy	2	1
Gastrointestinal system disorders		
Dry mouth	35	8
Constipation	8	4
Vomiting	3	1
Dyspepsia	4	3
Metabolic and nutritional disorders		
Increased appetite	5	3
Weight increased	3	< 1
Musculoskeletal and connective tissue disorders		
Back pain	3	2
Myalgia	3	2
Musculoskeletal stiffness	2	1
Psychiatric disorders		
Abnormal dreams	2	1
Respiratory disorders		
Nasal congestion	2	1
Special senses		
Vision blurred	3	2

* Events for which quetiapine fumarate extended-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.

b The following adverse events occurred in 1% of patients treated with quetiapine fumarate extended-release compared to < 1% in placebo: chills, dysarthria, dysgeusia, sluggishness, akathisia, dizziness postural, tachycardia, restless legs syndrome, gastroesoophageal reflux disease, pharyngolaryngeal pain and restlessness.

Table 5 enumerates the incidence of treatment-emergent adverse events that are dose related that occurred during acute monotherapy fixed dose studies (6-weeks) in ≥ 1% of patients

treated with quetiapine fumarate extended-release (50 - 300 mg/day) where the incidence of the adverse events in patients treated with quetiapine fumarate extended-release 150 mg and/or 300 mg was greater than the incidence in quetiapine fumarate extended-release 50 mg and placebo-treated patients.

Table 5 Dose Related Adverse Events in ≥ 1% of Patients Treated with Quetiapine fumarate extended-release (Doses 50, 150 and 300 mg/day) Where the Incidence of the Adverse Events in Patients Treated with Quetiapine Fumarate Extended-Release 150 mg and/or 300 mg was Greater than the Incidence in Quetiapine 50 mg and Placebo-Treated Patients in Short-Term Fixed Dose, Placebo-Controlled MDD Monotherapy Phase III Trials

Body System and MedDRA Term[a]	Percentage of Subjects with Adverse Events*			
	Placebo (n = 338)	Quetiapine Fumarate Extended-Release		
		50 mg (n = 181)	150 mg (n = 328)	300 mg (n = 331)
General disorders and administration site conditions				
Pain	0	1	1	2
Chills	0	1	0	2
Nervous system disorders				
Sedation	6	27	37	34
Somnolence	9	18	22	28
Dizziness	8	9	13	15
Dysarthria	0	1	1	3
Disturbance in attention	0	1	2	2
Hypoaesthesia	1	0	1	2
Akathisia	1	0	2	1
Lethargy	1	2	3	1
Paresthesia	1	1	2	1
Hypersomnia	0	1	2	1
Gastrointestinal system disorders				
Dry mouth	9	22	36	40
Constipation	4	7	7	9
Nausea	8	8	12	9
Vomiting	2	2	4	5
Dyspepsia	3	2	5	4
Gastroesophageal reflux disease	0	0	1	2
Abdominal distension	1	0	0	2
Abdominal pain	1	1	2	1
Cardiovascular disorders				

Body System and MedDRA Term[a]	Percentage of Subjects with Adverse Events*			
	Placebo (n = 338)	Quetiapine Fumarate Extended-Release		
		50 mg (n = 181)	150 mg (n = 328)	300 mg (n = 331)
Tachycardia	0	1	2	1
Metabolic and nutritional disorders				
Increased appetite	3	4	5	4
Weight increased	1	1	2	3
Musculoskeletal and connective tissue disorders				
Back pain	2	2	5	5
Arthralgia	2	2	3	3
Myalgia	2	4	5	3
Muscle tightness	1	1	0	2
Psychiatric disorders				
Anxiety	2	1	2	3
Abnormal dreams	3	2	4	2
Restlessness	0	0	1	2
Nightmare	1	1	1	2
Infections and infestations				
Nasopharyngitis	3	2	4	3
Gastroenteritis	0	1	2	1
Respiratory disorders				
Nasal congestion	2	1	2	3
Sinus congestion	1	1	2	2
Dyspnoea	1	1	1	2
Epistaxis	0	1	0	2
Nasal dryness	0	0	1	1
Special senses				
Vision blurred	1	2	3	5

* Events for which quetiapine fumarate extended-release incidence was equal to or less than placebo are not listed in the table.

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

Table 6 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute monotherapy (9 weeks) of elderly patients with MDD in ≥ 1% of patients treated with quetiapine fumarate extended-release (50 - 300 mg/day) where the incidence in patients treated with quetiapine fumarate extended-release was greater than the incidence in placebo-treated patients.

Table 6 Adverse Events Reported for at Least 1% of Quetiapine Fumarate Extended-Release - Treated Subjects (Doses ranging from 50 to 300 mg/day) and for a Higher Percentage of Quetiapine Fumarate Extended-Release -Treated Subjects than Subjects Who Received Placebo in a Short-Term, Placebo-Controlled Elderly MDD Monotherapy Phase III Trial

Body System and MedDRA Term[a,b]	Percentage of Subjects With Adverse Events*	
	Quetiapine fumarate extended-release (n = 166)	Placebo (n = 172)
General disorders and administration site conditions		
Fatigue	8	3
Asthenia	4	1
Nervous system disorders		
Somnolence	33	8
Headache	19	14
Dizziness	18	15
Sedation	5	1
Dysgeusia	2	1
Balance disorder	2	1
Dizziness postural	2	1
Akathisia	2	1
Gastrointestinal system disorders		
Dry mouth	20	10
Constipation	5	2
Abdominal pain upper	3	2
Dyspepsia	2	1
Cardiovascular system disorders		
Hypotension	2	0
Metabolic and nutritional disorders		
Weight increased	5	4
Weight decreased	2	1
Musculoskeletal and connective tissue disorders		
Back pain	2	1
Extrapyramidal disorder	4	1
Pain in extremity	2	1
Respiratory disorders		
Nasal congestion	2	0

* Events for which quetiapine fumarate extended-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.
b The following adverse events occurred in 1% of patients treated with quetiapine compared to < 1% in placebo: hypersomnia, restless legs syndrome, joint sprain, muscular weakness, pharyngolaryngeal pain and vision blurred.

Other Adverse Reactions

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, Endocrine and Metabolism – 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 α1 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 immediate-release formulation-treated patients compared to 2% in placebo-treated patients. Quetiapine immediate-release formulation 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: In schizophrenia trials, 0.8% of quetiapine fumarate extended-release patients, and no placebo patients, had tachycardia (> 120 bpm) at any time during the trials. In MDD monotherapy trials, 0.2% of quetiapine fumarate extended-release patients, and no placebo patients, had tachycardia (> 120 bpm) at any time during the trials. Quetiapine fumarate extended-release was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean decrease of 1 beat per minute for placebo. This is consistent with the rates of quetiapine immediate-release formulation.

This slight tendency to tachycardia may be related to the potential of quetiapine for inducing orthostatic changes (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular).

Extrapyramidal Symptoms (EPS): There have been very common cases of EPS reported. In three-arm, placebo-controlled clinical trials for the treatment of schizophrenia, utilizing doses between 300 mg and 800 mg of quetiapine fumarate extended-release tablets, the incidence of any adverse events potentially related to EPS was 7.5% for quetiapine fumarate extended-release tablets, 7.7% for quetiapine fumarate immediate-release tablets, and 4.7% in the placebo group and without evidence of dose response. In these studies, the incidence rates of the individual adverse events (e.g., akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) were generally low and did not exceed 3% for any treatment group.

At the end of treatment, the mean change from baseline in SAS total score and BARS Global Assessment score was similar across the treatment groups. The use of concomitant anticholinergic medications was infrequent and similar across the treatment groups.

The incidence of EPS was consistent with that seen with the profile of quetiapine immediate-release formulation in schizophrenia patients. The incidence of EPS did not increase with the dose of quetiapine fumarate extended-release tablets.

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 short-term, placebo-controlled monotherapy clinical trials in MDD the aggregated incidence of EPS was 5.4% for quetiapine fumarate extended-release and 3.2%

for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with MDD, the aggregated incidence of EPS was 9.0% for quetiapine fumarate extended-release and 2.3% for placebo. In long-term studies of schizophrenia, bipolar disorder and MDD 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: In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 12.1% for quetiapine and 6.7% for placebo. The aggregated incidence of the individual adverse events (e.g., insomnia, nausea, headache, diarrhea, vomiting, dizziness and irritability) did not exceed 5.3% in any treatment group and usually resolved 1 week after 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.

In these trials of patients with MDD the incidence of suicide related events was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo in patients 18-24 and 0.6% (11/1798) for quetiapine and 0.7% for placebo (7/1054) 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 NB-Quetiapine XR 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 extended-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 WARNINGS AND PRECAUTIONS, Special Populations).

Table 7 Adverse Drug Reactions in Children and Adolescents

Body System and MedDRA Term	**Percentage of Subjects With Adverse events**			
	quetiapine immediate-release formulation (n=340)a	Placebo in quetiapine immediate-release formulation studies (n=165)a	quetiapine fumarate extended-release 150-300 mg/day (n=92)b	Placebo in quetiapine fumarate extended-release studies (n=100)b
Metabolic and nutritional disorders				
Increased appetite	7.6	2.4	3.3	3.0
Investigations				
Prolactinc,d	13.4 (Male) 8.7 (Female)	4.0 (Male) 0.0 (Female)	N/A	N/A
Increases in blood pressure	15.2 (Systolic)e 40.6 (Diastolic)e	5.5 (Systolic)e 24.5 (Diastolic)e	6.5 (Systolic)f 46.7 (Diastolic)f	6.0 (Systolic)f 36.0 (Diastolic)f
Gastrointestinal disorders				

Body System and MedDRA Term	Percentage of Subjects With Adverse events			
Vomiting	6.5	5.5	3.3	3.0
Respiratory, thoracic, and mediastinal disorders				
Rhinitis	0.3	0.6	0.0	0.0
Nervous system disorders				
Syncope	1.5	0.0	1.1	0.0

a Based on pooled data from schizophrenia and mania pediatric placebo-controlled studies
b Based on data from Bipolar depression pediatric placebo-controlled study
c For quetiapine immediate-release formulation, prolactin levels (patients <18 years of age): >20 mcg/L males; >26 ug/L females at any time. Less than 1% of patients had an increase to a prolactin level of 100 mcg/L
d For quetiapine fumarate extended-release, prolactin values are not provided for Study D144AC00001 as values for this parameter are confounded and difficult to interpret due to the time intervening between randomized treatment and the recall visit.
e For quetiapine immediate-release formulation, based on shifts above clinically significant thresholds (adapted from the National Institute of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute weeks (3-6 weeks) placebo-controlled trials in children or adolescents. The"n" for the quetiapine immediate-release formulation arm was 335 and for the Placebo arm was 163.
f Based on increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time. Subjects were in the supine position.

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 immediate-release formulation group and -0.4 kg in the placebo group. Twenty one percent of quetiapine immediate-release formulation 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 group and 0.4 kg in the placebo group. Twelve percent of quetiapine immediate-release formulation 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 immediate-release formulation. 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 immediate-release formulation 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 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 immediate-release formulation 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 immediate-release formulation 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 immediate-release formulation 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 immediate-release formulation 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.

There have been no trials conducted in patients < 18 years of age with major depressive disorder.

rse Reactions

Seizures: There have been uncommon reports (≥ 0.1% - < 1%) 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 x 109/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.

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 x 109/L), granulocytopenia and agranulocytosis (severe neutropenia and infection) have been reported during antipsychotic use, including quetiapine fumarate extended-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 < 3 x 109 cells/L at any time (see 7 WARNINGS AND PRECAUTIONS, Hematologic). Based on shifts (eosinophil shifts were defined

as > 1 x 109 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, ≤ 100 x 109/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 mcg/L in males and > 30 mcg/L in females) (see 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hyperprolactinemia).

Neutropenia: In three-arm, quetiapine fumarate extended-release placebo-controlled monotherapy clinical trials, among patients with a baseline neutrophil count ≥ 1.5 x 109/L, the incidence of at least one occurrence of neutrophil count < 1.5 x 109/L was 1.5% in patients treated with quetiapine fumarate extended-release tablets and 1.5% for quetiapine immediate-release formulation, compared to 0.8% in placebo-treated patients.

In all short-term placebo-controlled monotherapy clinical trials among patients with a baseline neutrophil count ≥ 1.5 x 109 /L, the incidence of at least one occurrence of neutrophil count < 1.5 x 109 /L was 1.9% in patients treated with quetiapine, compared to 1.5% in placebo-treated patients. The incidence ≥ 0.5 - <1.0 x 109/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 109/L, among patients with a baseline neutrophil count ≥ 1.5 x 109/L, the incidence of at least one occurrence of neutrophil count < 0.5 x 109/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 T4, free T4, total T3 and free T3 <0.8 x LLN (pmol/L) and TSH > 5 mIU/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 T3 and common cases of decreases in total T4, free T4 and total T3 as well as increases in TSH have been reported. Table 8 shows the incidence of these shifts in short-term placebo-controlled clinical trials:

Table 8: 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 T3 and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T4 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 T4, 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, Endocrine and Metabolism, Hyperglycemia).

In two long-term bipolar maintenance placebo-controlled adjunct clinical trials, mean exposure 213 days for quetiapine immediate-release formulation (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 immediate-release formulation (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 immediate-release formulation) 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, Endocrine and Metabolism, 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 immediate-release formulation, which was driven by increases in LDL cholesterol. The mean LDL level increased at Week 24 by 10% in patients administered quetiapine immediate-release tablets, which was statistically significant. The total cholesterol/HDL ratio did not change significantly during therapy with quetiapine immediate-release formulation. Furthermore, triglycerides did not increase significantly nor did HDL cholesterol decrease during therapy. (See 7 WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Cholesterol and Triglyceride Elevations.)

The following adverse reactions were identified during post approval use of quetiapine fumarate extended-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 immediate-release formulation treatment. Resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine immediate-release formulation. 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 immediate-release formulation, 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 immediate-release formulation treatment. The reporting rate of anaphylaxis associated with quetiapine immediate-release formulation 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 WARNINGS AND PRECAUTIONS, 7.1 Special Populations).

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

In post-marketing reports, there have been cases of gastric bezoar formation in association with overdose of quetiapine (see 5 OVERDOSAGE).

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).

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 NB-Quetiapine XR to patients who are receiving other medications that have anticholinergic (muscarinic) properties and may affect voiding (see 7 WARNINGS AND PRECAUTIONS, Neurologic, Anticholinergic (muscarinic) effects).

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

The effect of NB-Quetiapine XR 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 co-administered with quetiapine immediate-release formulation.

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

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

Divalproex: Co-administration of quetiapine immediate-release formulation (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 NB-Quetiapine XR

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 immediate release formulation 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 NB-Quetiapine XR 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: CYP3A4 is the primary enzyme responsible for cytochrome P450-mediated metabolism of quetiapine. Thus, co-administration of compounds (such as ketoconazole, erythromycin, clarithromycin, diltiazem, verapamil, or nefazodone), which inhibit CYP3A4, 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 Cmax 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 tmax 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 CYP3A4 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 immediate-release formulation (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 immediate-release formulation following co-administration with cimetidine, (a non-specific P450 enzyme inhibitor), no clinically significant interaction was observed.

Thioridazine: Co-administration of thioridazine (200 mg bid) with quetiapine immediate-release formulation (300 mg bid), increased the clearance of quetiapine immediate-release formulation by 65%.

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

In patients taking the following antidepressants: amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine, addition of quetiapine fumarate extended-release (150 mg or 300 mg/day; for up to 4 weeks) did not appear to have a consistent overall effect on the trough or pre-dose plasma concentrations of the antidepressant.

NB-Quetiapine XR can be taken with or without food (see 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics).

Interactions with herbal products have not been established.

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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.

Quetiapine fumarate extended-release, a dibenzothiazepine derivative, is a psychotropic agent. Quetiapine and the active plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. It is the direct and indirect effects of quetiapine and norquetiapine that contribute to the pharmacological activity of quetiapine.

Quetiapine: Quetiapine exhibits affinity for brain serotonin 5HT2 and 5HT1A receptors (in vitro, Ki = 288 and 557 nM, respectively), and dopamine D1 and D2 receptors (in vitro, Ki = 558 and 531 nM, respectively). It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 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 H1 receptors (in vitro, Ki = 10 nM) and adrenergic α1 receptors (in vitro, Ki = 13 nM), with a lower affinity for adrenergic α2 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 D2 receptor blockade. The extent to which the norquetiapine metabolite contributes to the pharmacological activity of quetiapine 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 D2 receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D2 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-sensitized or drug-naive Cebus monkeys after acute and chronic administration.

Norquetiapine: Norquetiapine, similar to quetiapine, exhibits affinity for brain serotonin 5HT2 and $5HT_{1A}$ receptors (in vitro, Ki = 2.9 nM and 191 nM, respectively), and dopamine D1 and D2 receptors (in vitro, Ki = 42 nM and 191 nM respectively). Additionally, like quetiapine, norquetiapine also has high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 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 7 WARNINGS AND PRECAUTIONS, Neurologic, Anticholinergic (muscarinic) effects).

Inhibition of NET and partial agonist action at 5HT1A 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 5HT2B has been observed for norquetiapine, norquetiapine is found to be an antagonist and not an agonist at the receptor.

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. Quetiapine fumarate extended-release achieves peak plasma concentrations at approximately 6 hours after administration (Tmax). Quetiapine fumarate extended-release displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. The maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC) for quetiapine fumarate extended-release tablets administered once daily are comparable to those achieved for the same total daily dose of quetiapine immediate-release formulation administered twice daily. The mean plasma concentrations for each dose of quetiapine fumarate extended-release tablets versus 300 mg of quetiapine immediate-release formulation over a 24-hour dosing interval under fasting conditions are shown in Figure 1. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

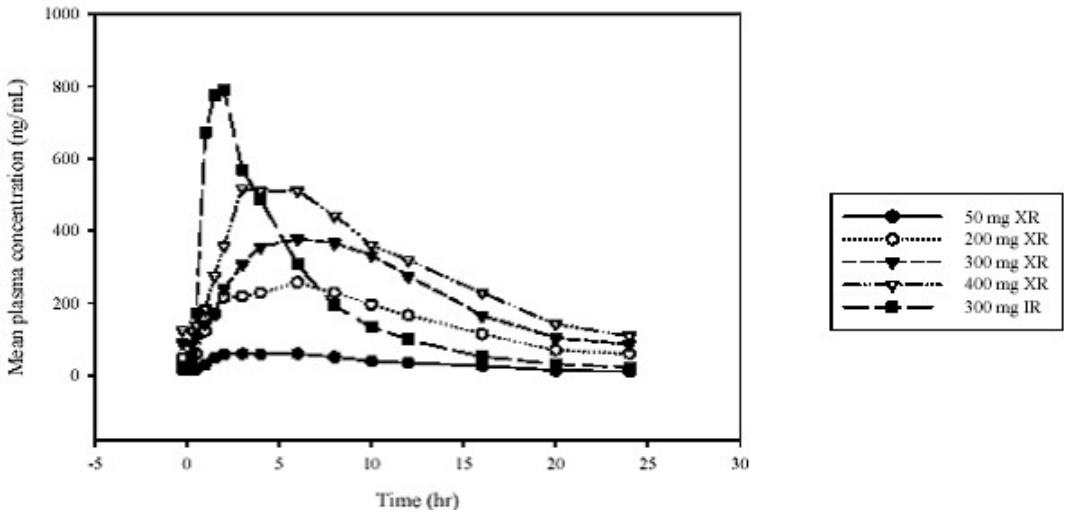


Figure 1: Mean quetiapine plasma concentrations (ng/mL) for each dose of quetiapine under fasted conditions versus time.

In a study (n=10) examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the quetiapine fumarate extended-release tablets Cmax and AUC of 44% to 52% and 20% to 22%, respectively, for the 50-mg and 300-mg tablets. In comparison, a light meal had no significant effect on the Cmax or AUC of quetiapine. This increase in exposure is not clinically significant, and therefore quetiapine fumarate extended-release tablets can be taken with or without food.

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

Metabolism: 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.

Elimination: The elimination half-life of quetiapine is approximately 6 - 7 hours upon multiple dosing within the proposed clinical dosage range. Quetiapine is extensively metabolized by the liver, with the 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 metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients. 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 WARNINGS AND PRECAUTIONS, 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 immediate-release formulation resulted in a 40% increase in both AUC and Cmax. Clearance of the drug decreased by 25% whereas t½ was elevated by nearly 45%. Therefore, quetiapine fumarate extended-release 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 immediate-release formulation in patients with moderate or severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic 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 m2). However, the individual clearance values remained within the range observed for healthy subjects (see 7 WARNINGS AND PRECAUTIONS, Renal and 4 DOSAGE AND ADMINISTRATION).

SPOSAL

NB-Quetiapine XR (quetiapine fumarate extended-release tablets) should be stored between 15°C - 30°C.

TIONS

Not Applicable.

PART II: SCIENTIFIC INFORMATION

ATION

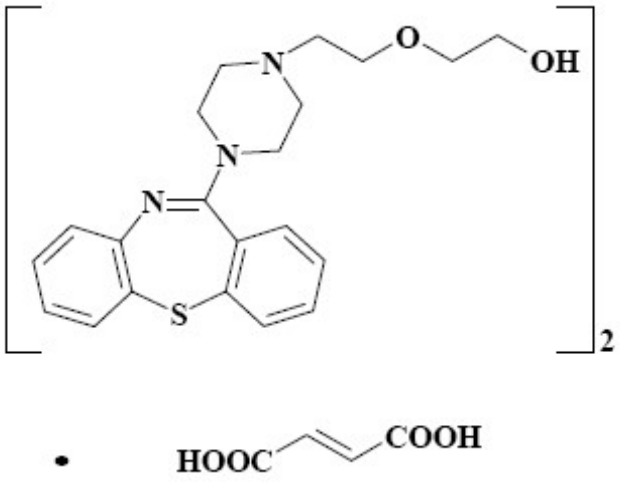
Drug Substance

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: [C21H25N3O2S]2 · C4H4O4 ; 883.1 g/mol

Structural formula:



Physicochemical properties: Quetiapine fumarate is a white or almost white crystalline powder. It is practically insoluble in water, freely soluble in glacial acetic acid, sparingly soluble in methanol and ethanol.

Ionization Constant: pKa1 = 3.3
pKa2 = 6.8

Melting Point: 172 - 176°C

Schizophrenia

The efficacy of quetiapine fumarate extended-release in the management of the manifestations of schizophrenia was supported by three short-term (6 week) placebo-controlled trials with inpatients and outpatients, and by one longer-term placebo-controlled trial of outpatients with schizophrenia who were clinically stable on quetiapine fumarate extended-release, and were then randomized to placebo or to remain on quetiapine fumarate extended-release.

Study Results:

1. A 6-week, placebo-controlled trial (n = 573) compared 3 doses of quetiapine fumarate extended-release (400, 600 and 800 mg), 1 dose of quetiapine immediate release formulation (400 mg), and placebo. Quetiapine fumarate extended-release administered once daily at doses of 400, 600 or 800 mg/day was statistically significantly superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score, PANSS response rate (at least 30 % reduction of PANSS total score from baseline), and the Clinical Global Impression Global Improvement (CGI-I) score at Day 42. The mean improvement on the PANSS total score compared to placebo was greater for quetiapine fumarate extended-release 600 mg (-12.1) and quetiapine fumarate extended-release 800 mg (-12.5) than quetiapine fumarate extended-release 400 mg (-6.1) or quetiapine immediate release formulation 400 mg (-7.8).

   The two highest doses of quetiapine fumarate extended-release (600 and 800 mg/day) were statistically significantly superior to placebo on the change in CGI Severity of Illness (CGI-S) score. All three quetiapine fumarate extended-release doses also demonstrated efficacy on a broad range of symptoms of schizophrenia as measured by the PANSS Positive and General Psychopathology subscale scores, and the PANSS aggression and hostility cluster score. The two highest doses of quetiapine fumarate extended-release also demonstrated statistically significant improvement compared to placebo on the PANSS Negative symptom subscale score and the PANSS depression cluster score.

2. In a longer-term study, clinically stable patients with schizophrenia who were being maintained on quetiapine fumarate extended-release (400 to 800 mg/day) for 16 weeks were randomized to either quetiapine fumarate extended-release (400 to 800 mg/day) or placebo. The mean dose of quetiapine fumarate extended-release was 669 mg. The primary endpoint was time to first psychiatric relapse. Patients treated with quetiapine fumarate extended-release experienced a significantly longer time to relapse following randomization compared to placebo. Significantly fewer patients treated with quetiapine fumarate extended-release experienced a relapse (11.7%) compared to

patients treated with placebo (48.5%) during the study. The estimated risk of relapse at 6 months was significantly reduced for patients treated with quetiapine fumarate extended-release (14.3%) compared to patients treated with placebo (68.2%).

3. A 6-week, placebo-controlled trial (n = 498) compared 3 doses of quetiapine fumarate extended-release (300, 600 and 800 mg), 2 doses of quetiapine immediate release formulation (300 and 600 mg), and placebo. Quetiapine fumarate extended-release administered once daily at 600 mg was statistically significantly superior to placebo on PANSS total score. Quetiapine fumarate extended-release 800 mg produced a numerically greater improvement, though not statistically significant, compared to placebo, as shown by a 2-fold greater decrease from baseline in PANSS total score. Quetiapine fumarate extended-release 800 mg was statistically significantly superior to placebo on the CGI-I score.

4. A 6-week, placebo-controlled trial (n = 544) compared 3 doses of quetiapine fumarate extended-release (400, 600 and 800 mg), 1 dose of quetiapine immediate release formulation (800 mg), and placebo. The quetiapine immediate release formulation dose and all quetiapine fumarate extended-release doses produced a numerically greater improvement, though not statistically significant, compared to placebo on the PANSS total score.

A combined statistical analysis of two of the short-term placebo-controlled studies (1 and 4 above) (n = 889) showed that quetiapine fumarate extended-release 600 and 800 mg were statistically significantly superior to placebo on the PANSS total score, PANSS response rate, CGI-I score and CGI-S score. Quetiapine fumarate extended-release 400 mg was statistically significantly superior to placebo on the PANSS total score, CGI-I score and CGI-S score, and was numerically greater, though not statistically significant, compared to placebo on the PANSS response rate.

Bipolar Disorder

Bipolar Mania

The efficacy of quetiapine fumarate extended-release in the management of manic episodes associated with bipolar disorder was established in one 3-week, placebo-controlled trial in bipolar patients with manic or mixed episodes with or without psychotic features (n = 316). Patients were hospitalized for a minimum of 4 days at randomization. Patients randomized to quetiapine fumarate extended-release received 300 mg on Day 1 and 600 mg on Day 2. Afterwards, the dose could be adjusted between 400 mg to 800 mg once daily.

The primary endpoint was the change from baseline in the Young Mania Rating Scale (YMRS) total score at Week 3.

Study Results:
Quetiapine fumarate extended-release at a dose of 400 to 800 mg/day for 3 weeks of treatment in patients with bipolar mania (both manic and mixed at baseline) was demonstrated to be statistically significant to placebo in reducing the level of manic symptoms as early as Day 4 and throughout the 3 weeks of treatment ($p \leq 0.003$).

Secondary endpoints also supported the superiority of quetiapine fumarate extended-release 400 to 800 mg/day over placebo in the treatment of mania in patients with bipolar disorder. Quetiapine fumarate extended-release was statistically significant over placebo at Week 3 in the proportion of patients showing ≥ 50% reduction in YMRS total score (responders) (55% vs 33%, $p < 0.001$) and the proportion of patients showing a YMRS total score ≤ 12 (remission) (42% vs 28%, $p = 0.006$). Quetiapine fumarate extended-release was also statistically significant over placebo on changes in Clinical Global Impression - Bipolar - Severity (CGI-BP-S) and Clinical Global Impression - Bipolar - Change (CGI-BP-C) overall illness scores at Week 3 ($p < 0.001$).

Quetiapine fumarate extended-release improved a range of symptoms at Week 3, including core symptoms of mania (including irritability, speech and thought content, $p \leq 0.011$), as assessed by the item analysis of the YMRS. The change in the MADRS score was statistically significant for quetiapine fumarate extended-release compared to placebo from Day 4 to Week 3 ($p \leq 0.042$).

For patients treated with quetiapine fumarate extended-release tablets, the mean daily dose over the treatment period was 604 mg with 47% having a final dose level of 600 mg/day, and approximately 22% and 29% of patients had final dose levels of 400 and 800 mg/day, respectively.

Bipolar Depression
The efficacy of quetiapine fumarate extended-release in the management of depressive episodes associated with bipolar disorder was established in one 8-week placebo-controlled study (n = 280 outpatients). This study included patients with bipolar I and II disorder with or without a rapid cycling course. Patients randomized to quetiapine fumarate extended-release were administered 300 mg once daily.

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

Study Results:
Quetiapine fumarate extended-release was demonstrated to be statistically significant versus placebo in reducing the level of depressive symptoms as early as Week 1 and throughout 8 weeks of treatment ($p < 0.001$). Bipolar I and bipolar II patients and patients with a rapid or non-rapid cycling course treated with quetiapine fumarate extended-release showed statistically significant greater improvements in MADRS total score compared to patients

treated with placebo.

The secondary endpoints supported the superiority of quetiapine fumarate extended-release over placebo. For most secondary endpoints the treatment advantage for quetiapine fumarate extended-release was apparent by Week 1 and continued through Week 8. For quetiapine fumarate extended-release tablets, the proportion of patients showing a MADRS total score ≤ 12 (remitters) was statistically significant versus placebo by Week 1 and continued to end-of-treatment ($p < 0.05$) (54% for quetiapine fumarate extended-release versus 39% for placebo at Week 8). Likewise, the proportion of patients showing ≥ 50% reduction in MADRS total score (responders) was statistically significant versus placebo by Week 2 and continued to end-of-treatment ($p \leq 0.007$) (65% for quetiapine fumarate extended-release versus 43% for placebo at Week 8). Quetiapine fumarate extended-release was also statistically significant over placebo on changes from baseline in CGI-BP-S for overall bipolar illness score (Week 8, $p < 0.001$) and in CGI-BP-C for overall illness score (Week 1 and throughout Week 8, $p < 0.001$).

Quetiapine fumarate extended-release significantly improved a broad range of symptoms (8 out of 10 items including core symptoms of depression) ($p < 0.05$), as assessed by an item analysis of the MADRS at Week 8.

There were fewer episodes of treatment-emergent mania with quetiapine fumarate extended-release (4.4%) than with placebo (6.4%).

In four 8-week bipolar depression trials, quetiapine immediate release formulation at doses of both 300 and 600 mg/day, was demonstrated to be statistically significant versus placebo in reducing depressive symptoms as measured by the change from baseline in the MADRS total score at Week 8 (primary endpoint), although no additional benefit was seen in the 600 mg group.

Major Depressive Disorder

The efficacy of quetiapine fumarate extended-release as a monotherapy treatment was assessed in 6 clinical trials in patients with major depressive disorder (MDD). Of these, 4 were acute monotherapy trials, 1 was a monotherapy elderly trial and 1 was a randomized withdrawal of treatment trial. All trials included patients who met DSM-IV criteria for MDD, single or recurrent episodes, with and without psychotic features.

<u>Acute Monotherapy</u>

The efficacy of quetiapine fumarate extended-release as monotherapy in the treatment of MDD was assessed in two 6-week placebo-controlled fixed dose trials, and two 8-week placebo-controlled modified fixed dose trials (optional one time dose increase). In addition, the efficacy of quetiapine fumarate extended-release was assessed in non-demented elderly patients (aged 66 to 89 years) in one 9-week placebo-controlled flexible dose trial (mean dose 160 mg/day).

The study designs are summarized in Table 9.

Table 9 Study Design of Clinical Trials Supporting Efficacy of Quetiapine Fumarate Extended-Release in the Monotherapy Treatment of MDD

Study #	Study Type	Treatment Arms (Once Daily)	Duration of Treatment	Study Subjects (N)[a]	Baseline MADRS Score
1	Fixed dose	Quetiapine fumarate extended-release 50 mg Quetiapine fumarate extended-release 150 mg Quetiapine fumarate extended-release 300 mg Placebo	6 weeks	700	30.7
2	Fixed dose	Quetiapine fumarate extended-release 150 mg Quetiapine fumarate extended-release 300 mg Duloxetine 60 mg Placebo	6 weeks	587	30.1
3	Modified Fixed dose	Quetiapine fumarate extended-release 150/300 mg Placebo	8 weeks	299	29.5
4	Modified Fixed dose	Quetiapine fumarate extended-release 150/300 mg Escitalopram 10/20 mg Placebo	8 weeks	459	31.9
14	Flexible dose (elderly)	Quetiapine fumarate extended-release 50-300 mg Placebo	9 weeks	335	27.9

a Number of patients who took at least 1 dose of investigational product and had a randomization MADRS assessment and at least 1 valid MADRS assessment after randomization.

The primary endpoint in these trials was the change from baseline to week 6 (Study 1 and 2), or 8 (Study 3 and 4) or 9 (Study 14) in the Montgomery-Asberg Depression Rating Scale (MADRS),

a 10 item clinician-rated scale used to assess the degree of depressive symptomatology. A Hamilton Rating Scale for Depression (HAM-D-17) total score of ≥ 22 was a requirement for study entry. The mean HAM-D total score at entry was 26.

Study Results:

Acute Monotherapy

Quetiapine fumarate extended-release was statistically superior to placebo in reduction of depressive symptoms as measured by change in MADRS total score (Table 10).

Secondary endpoints also supported the superiority of quetiapine fumarate extended-release 50 to 300 mg/day over placebo in the monotherapy treatment of MDD (Table 10).

In the fifth trial (Study 4), neither quetiapine fumarate extended-release nor the active comparator (escitalopram) were statistically significant compared to placebo on the MADRS total score as well as on the key secondary endpoints.

Table 10 Efficacy of Quetiapine Fumarate Extended-Release in the Acute Monotherapy Treatment of MDD

Treatment Arms (Once Daily)	MADRS Total Score (Primary Endpoint	MADRS Response (≥ 50% Reduction)*	HAM-D Total Score	HAM-D Item 1	HAM-A Total Score	CGI-S Score	% Improved on CGI
Study 1							
Quetiapine fumarate extended-release 50	-13.56c	42.7%b	-12.35	-1.34	-8.11c	-1.43c	52.8%b
mg Quetiapine fumarate extended-	-14.50b	51.2%a	-12.84c	-1.45c	-8.34b	-1.50b	54.2%b
release 150 mg Quetiapine fumarate	-14.18b	44.9%a	-12.65c	-1.48c	-8.20c	-1.49b	54.0%b
extended-release 300 mg Placebo	-11.07	30.3%	-10.93	-1.18	-6.64	-1.11	39.3%
Study 2							
Quetiapine fumarate extended-release 150	-14.81a	54.4%b	-13.12a	-1.49a	-7.76b	-1.43b	54.1%c
mg Quetiapine fumarate extended-	-15.29a	55.1%a	-14.02a	-1.56a	-7.38b	-1.60a	59.2%a
release 300 mg	-14.64a	49.6%c	-12.37c	-1.53a	-7.83a	-1.53a	56.7%b
Duloxetine 60 mg	-11.18	36.2%	-10.26	-1.07	-5.55	-1.06	39.5%
Placebo							
Study 3							
Quetiapine fumarate	-16.49b	61.9%c	-14.75c	-1.71c	-9.14c	-1.64b	63.3%c

Treatment Arms (Once Daily)	MADRS Total Score (Primary Endpoint	MADRS Response (≥ 50% Reduction)*	HAM-D Total Score	HAM-D Item 1	HAM-A Total Score	CGI-S Score	% Improved on CGI
extended-release 150/300 mg Placebo	-13.1	48.0%	-12.35	-1.40	-7.70	-1.24	52.0%
Study 14 Quetiapine fumarate extended-release 50-300 mg Placebo	-16.33a -8.79	64.0%a 30.4%	-15.66a -8.62	-1.84a -1.13	-10.51a -5.20	-1.73a -0.77	71.3%a 39.2%

* Response is defined as ≥ 50% reduction in the MADRS total score from baseline.

a $p \leq 0.001$ comparison with placebo.

b $p < 0.01$ comparison with placebo.

c $p < 0.05$ comparison with placebo.

Longer-Term Randomized Withdrawal Study

The efficacy of quetiapine fumarate extended-release in maintaining treatment of MDD was assessed in a longer-term clinical trial, which consisted of open-label treatment with quetiapine fumarate extended-release followed by a double-blind randomized placebo-controlled treatment phase. Patients who had a HAM-D total score of ≥ 20 received quetiapine fumarate extended-release (flexibly dosed at 50 mg, 150 mg, or 300 mg once daily) for 4 to 8 weeks. Patients who responded (CGI-S ≤ 3 and a MADRS total score ≤ 12) received open-label quetiapine fumarate extended-release for an additional 12 to 18 weeks, within the same dose range.

Patients who responded during the additional open label treatment period and who met the criteria for randomization (CGI-S ≤ 3 and a MADRS total score ≤ 12) were randomized to placebo (n = 385) or to continue on quetiapine fumarate extended-release (n = 391) for up to 52 weeks (median duration of exposure to quetiapine fumarate extended-release was 158 days (mean 167 days); 15 patients completed the entire 52 weeks). Relapse or a depressed event during the double-blind phase was defined as: initiation of pharmacological treatment by the investigator, other than the allowed hypnotics, to treat depressive symptoms; initiation of pharmacological treatment by the patient for at least 1 week, other than the allowed hypnotics, to treat depressive symptoms; hospitalization for depressive symptoms; MADRS score ≥ 18 at 2 consecutive assessments 1 week apart, or at the final assessment if the patient discontinued; CGI-S score ≥ 5; suicide attempt or discontinuation from study due to imminent risk of suicide.

Longer-term Randomized Withdrawal Study

Quetiapine fumarate extended-release (mean dose 177 mg/day) significantly increased the time to a depressed event compared with placebo (primary endpoint) and significantly fewer patients treated with quetiapine fumarate extended-release experienced a relapse (14.2%) compared to patients treated with placebo (34.4%) during the study (Hazard ratio 0.34, i.e., the risk of recurrence of depressive event was reduced by 66%; 95% CI 0.25, 0.46; p-value < 0.001 versus placebo) (see Figure 2).

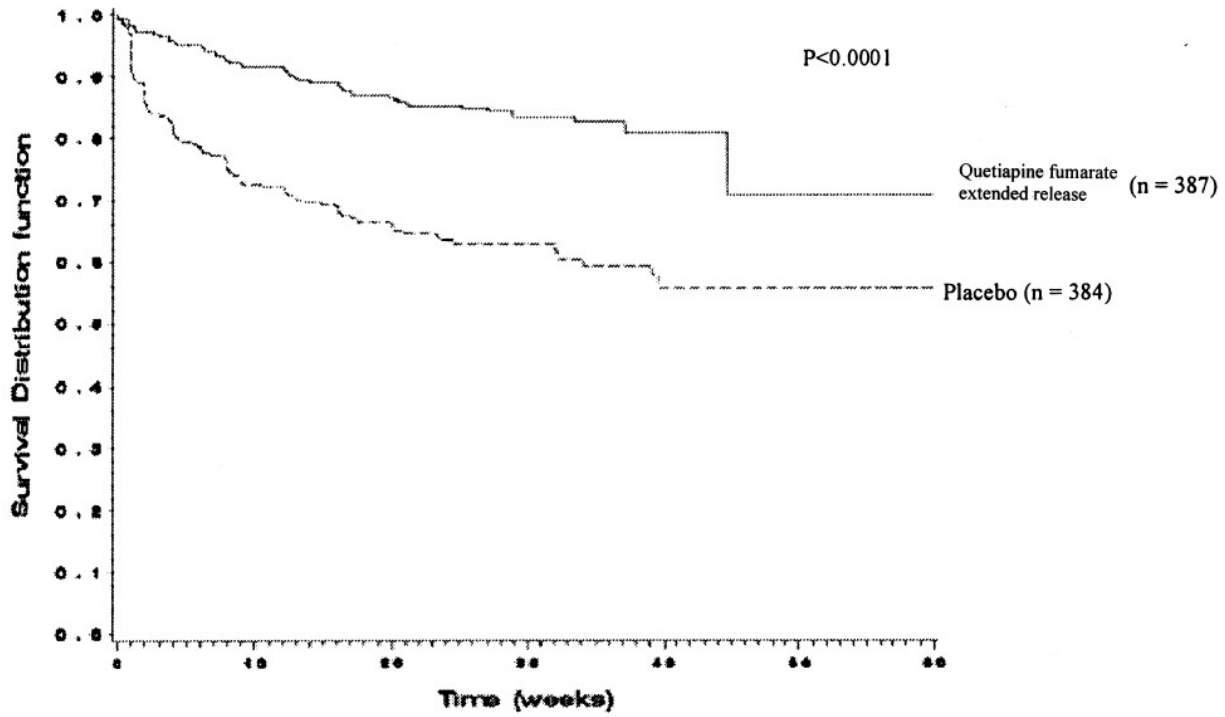


Figure 2: Time to a depressed event, Longer-Term Randomized Withdrawal Study, Kaplan Meier curves (ITT population)

ies

A blinded, single-dose, randomised, 2-way cross-over bioequivalence study of NB-Quetiapine XR (quetiapine fumarate extended release tablet, NB Pharma Inc.) and Seroquel XR® (quetiapine fumarate extended release tablet, AstraZeneca Canada Inc.) following a single 50 mg dose was conducted in healthy male (26) and female (10) subjects, 19 to 40 years of age, under fasted conditions. A summary of the pharmacokinetic parameters from the 35 volunteers included in the bioavailability comparison is tabulated below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Quetiapine (1 x 50 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means1	90% Confidence Interval 1
AUC0-t (ng.h/mL)	417.88 468.52 (48.21)	473.57 529.12 (47.57)	88.24%	81.89% to 95.08%
AUC0-inf (ng.h/mL)	430.93 481.55 (47.67)	493.19 551.76 (48.10)	87.38%	81.33% to 93.87%
AUC0-24 (ng.h/mL)	392.46 437.36 (47.29)	422.12 468.40 (45.44)	92.97%	86.24% to 100.23%
Cmax (ng/mL)	41.60 46.86 (52.85)	36.55 40.95 (46.25)	113.80%	101.17% to 128.00%
Tmax§ (h)	4.42 (23.66)	7.08 (37.26)		
T½ el§ (h)	6.02 (24.75)	6.30 (28.02)		

* Quetiapine fumarate extended-release tablets (manufactured for NB Pharma Inc.)

† Seroquel XR (manufactured by AstraZeneca Canada Inc. and purchased in Canada)

§ Expressed as the arithmetic mean (CV%) only

1 Based on least-squares mean estimates

A blinded, single-dose, randomised, 2-way cross-over bioequivalence study of NB-Quetiapine XR (quetiapine fumarate extended release tablet, NB Pharma Inc.) and Seroquel XR® (quetiapine fumarate extended release tablet, AstraZeneca Canada Inc.) following a single 50 mg dose was conducted in healthy male (51) and female (17) subjects, 19 to 40 years of age, under fed conditions. A summary of the pharmacokinetic parameters from the 66 volunteers included in the bioavailability comparison is tabulated below.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Quetiapine (1 x 50 mg) From measured data Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means1	90% Confidence Interval 1
AUC0-t (ng.h/mL)	607.02 667.34 (46.40)	608.09 664.52 (46.49)	99.82	95.13 to 104.75
AUC0-inf (ng.h/mL)	618.96 679.38 (46.18)	622.99 680.87 (46.79)	99.35	94.75 to 104.18
AUC0-24 (ng.h/mL)	596.11 650.81 (44.73)	589.44 639.65 (44.87)	101.13	96.48 to 106.01
Cmax (ng/mL)	85.57 92.44 (42.52)	81.76 89.08 (45.92)	104.66	96.81 to 113.14
Tmax§ (h)	4.52 (17.10)	5.66 (31.72)		
T½ el§ (h)	4.74 (13.88)	4.87 (20.31)		

* Quetiapine fumarate extended-release tablets (manufactured for NB Pharma Inc.)
† Seroquel XR (manufactured by AstraZeneca Canada Inc. and purchased in Canada)
§ Expressed as the arithmetic mean (CV%) only
1 Based on least-squares mean estimates

A blinded, single-dose, randomized, two-way crossover comparative bioequivalence study of NB-Quetiapine XR (quetiapine fumarate, NB Pharma Inc.) and Seroquel XR® (quetiapine fumarate, AstraZeneca Canada Inc.) following a single 200 mg dose in healthy male (18) and female (17) subjects, 20 to 40 years of age, under fasting conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Quetiapine (1 x 200 mg) From measured data Geometric Mean2 Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means1	90% Confidence Interval1
AUC0-t (ng.h/mL)	1925.20 2050.06 (37.63)	2089.84 2232.04 (38.05)	92.12%	88.05% to 96.38%
AUC0-inf (ng.h/mL)	1996.44 2127.42 (37.77)	2233.66 2416.21 (43.87)	89.38%	84.76% to 94.25%
Cmax (ng/mL)	167.99 183.82 (45.62)	162.63 176.61 (47.63)	103.29%	93.19% to 114.49%
Tmax (h)	4.47 (39.37)	6.72 (47.68)		
T½ el (h)	6.96 (24.89)	7.85 (43.37)		

* Quetiapine fumarate extended-release tablets (manufactured for NB Pharma Inc.)

† Seroquel XR (manufactured by AstraZeneca Canada Inc. and purchased in Canada)

1 Based on least-squares mean estimates

2 Geometric least-squares mean are presented for unbalanced study

A blinded, single-dose, randomized, two-way crossover comparative bioequivalence study of NB-Quetiapine XR (quetiapine fumarate, NB Pharma Inc.) and Seroquel XR® (quetiapine fumarate, AstraZeneca Canada Inc.) following a single 200 mg dose in healthy male (17) and female (16) subjects, 18 to 40 years of age, under fed conditions.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Quetiapine (1 x 200 mg) From measured data Geometric Mean2 Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means1	90% Confidence Interval 1
AUC0-t (ng.h/mL)	2315.56 2579.19 (50.64)	2207.80 2422.97 (42.69)	104.88%	99.12% to 110.98%
AUC0-inf (ng.h/mL)	2339.01 2606.16 (51.00)	2243.31 2467.11 (43.48)	104.27%	98.65% to 110.20%
Cmax (ng/mL)	304.90 332.31 (43.12)	279.34 310.82 (45.00)	109.15%	99.37% to 119.89%
Tmax (h)	4.39 (17.24)	5.78 (32.92)		
T½ el (h)	4.71 (17.55)	4.77 (26.59)		

* Quetiapine fumarate extended-release tablets (manufactured for NB Pharma Inc.)

† Seroquel XR (manufactured by AstraZeneca Canada Inc. and purchased in Canada)

1 Based on least-squares mean estimates

2 Geometric least-squares mean are presented for unbalanced study

No microbiological information is required for this drug product.

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/m2 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/m2 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/m2 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 11 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 D2 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 12.

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 13.

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 11 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).
Dog Beagle	oral tablets	4 weeks	3	0 25 50	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-

				100	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.

Table 11 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	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.
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.
Cynomolgus monkey	oral gavage	56 weeks dosing	4	0, rising dose for 4 weeks	Dose-related incidence and severity of behavioural changes. No abnormal signs on drug withdrawal. 40 - 60% reduction in

		4 weeks withdrawal		then 25, 100 and 225 mg/kg/day administered as 3 doses/day	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 12 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, 400-1100 (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.
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 13 Reproduction and Teratology Studies With Quetiapine

Species/Strain	Route	Study Duration	Number/ Group	Dose (mg/kg/day)	Salient Observations
Rat Alpk:AP$_f$SD 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:AP$_f$SD 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 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:AP$_f$SD 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.
Rat Crj: Wistar	Oral	21 days females	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

Segment II Teratology		dosed from d6 to d15 gestation			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.

Table 13 Reproduction and Teratology Studies With Quetiapine

Species/Strain	Route	Study Duration	Number/ Group	Dose (mg/kg/day)	Salient Observations
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

Pr SEROQUEL XR®, Tablets 50mg, 150mg, 200mg, 300mg, and 400mg, Submission Control Number: 255494 Product Monograph, AstraZeneca Canada Inc. January 4, 2022.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]NB-Quetiapine XR
quetiapine fumarate extended-release tablets

Read this carefully before you start taking **NB-Quetiapine XR** 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 **NB-Quetiapine XR.**

Serious Warnings and Precautions

- NB-Quetiapine XR 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)
- NB-Quetiapine XR is not to be used if you are elderly and have dementia.

What is NB-Quetiapine XR used for?
NB-Quetiapine XR (quetiapine fumarate extended-release tablets) is used to treat the 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 (feeling, hearing, seeing 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

NB-Quetiapine XR 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 vey quickly, too loudly, or more than usual
- needing less sleep
- having poor judgement
- severe irritability
- feeling sad or hopeless
- loss of interest and enjoyment
- feeling tired

NB-Quetiapine XR is also used to treat symptoms of depression in adults when taken with your current antidepressant medication. It is prescribed when you do not respond adequately to an antidepressant alone and after you have tried other antidepressant treatments. Some of the common symptoms of depression may include:

- feeling sad or hopeless
- loss of interest and enjoyment
- a change in appetite or weight
- difficulty concentrating or sleeping
- feeling tired
- headaches
- unexplained aches and pain

NB-Quetiapine XR is not a cure for your condition but it can help manage your symptoms and help you feel better.

How does NB-Quetiapine XR 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 NB-Quetiapine XR works is unknown, however it seems to adjust the balance of these chemicals.

What are the ingredients in NB-Quetiapine XR?
Medicinal ingredients: Quetiapine fumarate.
Non-medicinal ingredients: Colloidal silicon dioxide, hydrogenated vegetable oil, lactitol, lactose monohydrate, magnesium stearate, polyethylene glycol, polyvinyl alcohol, red iron oxide (50 mg tablets only), succinic acid, talc, titanium dioxide and yellow iron oxide (50 mg, 200 mg and 300 mg tablets only).

NB-Quetiapine XR comes in the following dosage forms:
Extended Release tablets: 50 mg (capsule shape, peach colour), 150 mg (capsule shape, white colour), 200 mg (capsule shape, yellow colour), 300 mg (capsule shape, pale yellow colour) and 400 mg (capsule shape, white colour).

Do not use NB-Quetiapine XR if:

- you are allergic to quetiapine fumarate or any of the ingredients listed in the "nonmedicinal ingredients" section of this leaflet.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NB-Quetiapine XR. 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 NB-Quetiapine XR.
- 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 a stroke
- have or have a family history of:
    - heart problems
    - any problems with how your heart beats
    - heart disease
- have a history of seizures (fits)
- have diabetes or a family history of diabetes, as NB-Quetiapine XR 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, 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 quetiapine fumarate extended-release tablets 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 your treatment with NB-Quetiapine XR 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 NB-Quetiapine XR.

- 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: NB-Quetiapine XR may make you feel sleepy. Give yourself time after taking NB-Quetiapine XR 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 NB-Quetiapine XR treatment is related to these problems.

NB-Quetiapine XR 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 NB-Quetiapine XR:

- NB-Quetiapine XR can increase the effects of 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
- Medicines that affect the way your heart beats, these include drugs known to cause electrolyte imbalance called “diuretics” (water pills)
- 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.
- Drugs called “protease inhibitors” used to treat Human Immunodeficiency Virus (HIV).

Effect on Urine Drug Screens: NB-Quetiapine XR 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 NB-Quetiapine XR so more specific tests can be conducted.

How to take NB-Quetiapine XR:

- Even if you feel better, do NOT stop taking NB-Quetiapine XR or change your dose without talking to your doctor first.
- Try to take NB-Quetiapine XR at the same time each day
- NB-Quetiapine XR can be taken with or without food
- Swallow tablets whole, do NOT split, crush, or chew

Usual dose:

Schizophrenia and Bipolar Mania
The usual dosing schedule is 300 mg on day 1, 600 mg on day 2, and up to 800 mg on day 3 and onwards taken once daily. The maximum dose is 800 mg per day.

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

Major Depressive Disorder
The usual dosing schedule is 50 mg on days 1 and 2 and 150 mg on day 3. Your doctor may adjust the dose upwards or downwards within the recommended dose range of 50 - 300 mg per day during the course of your treatment depending on your response and tolerability.

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 NB-Quetiapine XR or change the times of day you take NB-Quetiapine XR without talking to your doctor first.

If you stop taking NB-Quetiapine XR 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 NB-Quetiapine XR for you.

Overdose:

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

Missed Dose:
NB-Quetiapine XR should be taken at the same time each day. If you miss a dose from the previous day, you should take your next regular dose of NB-Quetiapine XR the next day at the normal time. Do not take two tablets to make up for a missed dose

What are possible side effects from using NB-Quetiapine XR?
These are not all the possible side effects you may have when taking NB-Quetiapine XR. 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
- Dry mouth
- Blurred vision
- Difficulty swallowing
- Feeling more hungry
- Weight gain
- Trouble sleeping or falling asleep
- Abnormal dreams and nightmares
- Problems with speech or language

If you take more NB-Quetiapine XR than you should, a gum-like sticky mass of tablets may form in your stomach. Please contact your doctor immediately as it may require removal.

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, 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).		✓	

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**	
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		✓	

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**	
but will then last, nausea and vomiting, constipation or diarrhea.			
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		✓	

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**	
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		✓	
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, tell 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/adverse-reaction-reporting.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 NB-Quetiapine XR 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 NB-Quetiapine XR or you find that it has passed its expiry date, please return any left over medicine to your pharmacist.

Keep out of reach and sight of children.

If you want more information about NB-Quetiapine XR:

- 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.nbpharmainc.com, or 1-855-662-1814.

This leaflet was prepared by NB Pharma Inc.

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