PRODUCT MONOGRAPH

[Pr]AVA-QUETIAPINE

Quetiapine as Quetiapine Fumarate

Tablets 25 mg, 100 mg, and 200 mg

Antipsychotic Agent

AVANSTRA INC.
10761-25th NE
Suite 110, Building "B",
Calgary, Alberta, T2C 3C2

DATE OF PREPARATION:
February 16, 2011

Control #144981

Table of Contents

[Pr]AVA-QUETIAPINE
Quetiapine Fumarate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablet / 25 mg, 100 mg, and 200 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Schizophrenia
AVA-QUETIAPINE (quetiapine) is indicated for the management of the manifestations of schizophrenia. The antipsychotic efficacy of quetiapine was established in short-term (6-week) controlled inpatient trials (see Part II: CLINICAL TRIALS). The efficacy of quetiapine in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials of patients with manifestations of schizophrenia.

Bipolar Disorder – Mania
AVA-QUETIAPINE is indicated as monotherapy for the acute management of manic episodes associated with bipolar disorder.

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

Geriatrics (> 65 years of age)
AVA-QUETIAPINE is not indicated in elderly patients with dementia. See WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions Box and Special Populations.

Pediatrics (< 18 years of age)
The safety and efficacy of AVA-QUETIAPINE in children under the age of 18 years have not been established.

CONTRAINDICATIONS

AVA-QUETIAPINE (quetiapine) is contraindicated in patients with a known hypersensitivity to this medication or any of its ingredients. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

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 WARNINGS AND PRECAUTIONS, Special Populations, Use in Geriatric Patients with Dementia).

General

Body Temperature Regulation: Although not reported with quetiapine disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing AVA-QUETIAPINE 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.

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

Carcinogenesis and Mutagenesis

For animal data, see Part II: TOXICOLOGY.

Cardiovascular

Hypotension and Syncope: As with other drugs that have high α_1 adrenergic receptor blocking activity, quetiapine may induce orthostatic hypotension, dizziness, and sometimes syncope, especially during the initial dose titration period. Syncope was reported in 1% (23/2371) of patients treated with quetiapine, compared with 0% (0/404) on placebo, and 0.4% (2/527) on active control drugs. The risk of hypotension and syncope may be reduced by more gradual titration to the target dose (see DOSAGE AND ADMINISTRATION).

Quetiapine should be used with caution in patients with known cardiovascular disease (e.g., history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or other conditions predisposing to hypotension (e.g., dehydration, hypovolemia and treatment with antihypertensive medications) (see OVERDOSAGE).

Cholesterol and Triglyceride Elevations: In short-term placebo-controlled schizophrenia trials, quetiapine-treated patients showed mean increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to mean decreases in the placebo-treated patients. LDL cholesterol was not measured in these trials.

Very common (≥10%) cases of elevations in serum triglyceride levels (≥2.258 mmol/L on at least one occasion) and elevations in total cholesterol (predominantly LDL cholesterol) (≥6.2064 mmol/L on at least one occasion) have been observed during treatment with quetiapine in clinical trials (see ADVERSE REACTIONS). Lipid increases should be managed as clinically appropriate.

Endocrine and Metabolism

Hyperglycaemia: As with some other antipsychotics, hyperglycaemia 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 hyperglycaemia (see ADVERSE REACTIONS, Post-Market Adverse Drug Reactions).

Increases in blood glucose and hyperglycaemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings).

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 hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemiarelated 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.

Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Hyperprolactinemia: Elevation of prolactin levels was not seen in clinical trials with quetiapine, although increased prolactin levels were observed in rat studies with this compound. 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.

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

Hypothyroidism: Clinical trials in schizophrenia demonstrated that quetiapine is associated with a dose-related decrease in total and free thyroxine (T_4). On average quetiapine was associated with about a 20% mean reduction in thyroxine levels (both total and free). Forty-two percent of quetiapine-treated patients showed at least a 30% reduction in total T_4 and 7% showed at least a 50% reduction. Maximum reduction of thyroxine levels generally occurred during the first two to four weeks of treatment with quetiapine. These reductions were maintained without adaptation or progression during longer term treatment. Decreases in T_4 were not associated with systematic changes in TSH or clinical signs or symptoms of hypothyroidism. Approximately 0.4% 12/2595) of patients treated with quetiapine (schizophrenia and bipolar studies combined) experienced persistent increases in TSH, and 0.25% of patients were treated with thyroid replacement.

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

In the acute placebo-controlled bipolar mania clinical trials (up to 12 weeks) mean weight gain in patients taking quetiapine was 1.8 kg compared to a mean weight loss of 0.1 kg in patients taking placebo. In patients completing the entire 12 weeks of treatment mean weight gain in patients taking quetiapine was 2.8 kg.

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.

Hematologic

Neutropenia: Severe neutropenia ($<0.5 \times 10^9$/L) has been uncommonly reported in quetiapine clinical trials. There was no apparent dose relationship. Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count (WBC) and history of drug induced leucopenia and/or neutropenia. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9$/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5×10^9/L). (See ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings and Post-Market Adverse Drug Reactions).

Hepatic

Hepatic Impairment: Decreased clearance of quetiapine was observed in patients with mild hepatic impairment (see ACTIONS and CLINICAL PHARMACOLOGY, Special Populations and Conditions). Patients with mild hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25 to 50 mg/day to an effective dose, depending on the clinical response and tolerability in the individual patient. No pharmacokinetic data are available for any dose of quetiapine 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 ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions and DOSAGE AND ADMINISTRATION).

Transaminase Elevations: During premarketing clinical trials, therapy with quetiapine was associated with elevation of hepatic transaminases, primarily ALT. Within a clinical trial database of 1892 quetiapine-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 -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 therapy. Of the 101 quetiapine-treated patients whose enzyme levels increased to >120 IU/L, 40 discontinued treatment while their ALT values were still raised. In 114 quetiapine–treated patients whose baseline ALT was >90 IU/L, only 1 experienced an elevation to >400 IU/L.

In the bipolar disorder - mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range, was approximately 1% for both quetiapine-treated and placebo-treated patients.

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

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.

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. 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.

It has been hypothesized that agents with a lower EPS liability may also have a lower liability to produce TD. In schizophrenia and bipolar mania placebo-controlled clinical trials with quetiapine, the incidence of EPS was not statistically significantly different than placebo across the recommended therapeutic dose range. This may predict that quetiapine has less potential than standard antipsychotic agents to induce TD in schizophrenia and bipolar mania patients (see 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, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of the syndrome.

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

Potential Effect on Cognitive and Motor Performance: Somnolence was a 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.

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 treatment, but a causal relationship to quetiapine use has not been established. The possibility of lenticular changes during long-term use of quetiapine in man, thus can not be excluded at this time. Eye examinations (e.g., slit lamp exam) prior to or shortly after initiation of treatment with quetiapine and at 6 month intervals thereafter, are recommended. If clinically significant lens changes associated with quetiapine use are observed, discontinuation of quetiapine should be considered.**

Psychiatric

Suicide: The possibility of suicide or attempted suicide is inherent in bipolar disorder and schizophrenia, and thus close supervision and appropriate clinical management of high-risk patients should accompany drug therapy.

Renal

There is little experience with quetiapine in patients with renal impairment, except in a low (subclinical) single dose study (see ACTIONS AND CLINICAL PHARMACOLOGY, Special Populations and Conditions). Quetiapine should thus be used with caution in patients with known renal impairment, especially during the initial dosing period (see DOSAGE AND ADMINISTRATION).

Special Populations

Pregnant Women: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with quetiapine. The safety and efficacy of quetiapine during human pregnancy have not been established. Therefore, quetiapine should only be used during pregnancy if the expected benefits justify the potential risks.

Nursing Women: The degree to which quetiapine is excreted into human milk is unknown. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine.

Pediatrics (< 18 years of age): The safety and efficacy of quetiapine in children under the age of 18 years have not been established.

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

Use in Geriatric Patients with Dementia:
Overall Mortality: Elderly patients with dementia treated with atypical antipsychotic drugs showed increased mortality compared to placebo in a meta-analysis of 13 controlled trials of various atypical antipsychotic drugs. 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.
Quetiapine is not indicated in elderly patients with dementia.

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

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.

Clinical Trial Adverse Drug Reactions

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

Adverse Events Associated with Discontinuation

Short-Term Placebo-Controlled Clinical Trials:

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

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

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

Commonly Observed Adverse Events in Short-Term Placebo-Controlled Clinical Trials
Schizophrenia: The following treatment-emergent adverse events, derived from Table 1, commonly occurred during acute therapy with quetiapine (incidence of at least 5%, and an incidence at least 5% higher than that observed with placebo): somnolence, dizziness, dry mouth, postural hypotension, and elevated ALT levels.

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

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

Table 1 Adverse Events Reported For At Least 1% Of Quetiapine-Treated Subjects (Dose ≥ 150 mg/day) And For A Higher Percentage Of Quetiapine-Treated Subjects Than Subjects Who received Placebo In Short-Term, Placebo-Controlled Schizophrenia Phase II-III Trials

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

* Subjects may have had more than one adverse event.

Other Adverse Events

Weight Gain: During acute therapy (up to 6 weeks) in placebo-controlled schizophrenia clinical trials, mean weight gain in patients taking quetiapine was 2.3 kilograms compared to a mean weight gain of 0.1 kilograms in patients taking placebo. In open-label extension trials with quetiapine monotherapy, mean weight gain after 9 to 13 weeks was 1.58 kg, after 14 to 26 weeks, 0.26 kg, after 27 to 39 weeks, 1.66 kg, after 40 to 52 weeks, -1.53 kg and after 53 to 78 weeks, 1.98 kg (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). In the acute placebo-controlled bipolar mania clinical trials (up to 12 weeks) mean weight gain in patients taking quetiapine was 1.8 kg compared to a mean weight loss of 0.1 kg in patients taking placebo. In patients completing the entire 12 weeks of treatment mean weight gain in patients taking quetiapine was 2.8 kg.

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 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 (≥0.01% - <0.1%) of priapism in patients administered quetiapine.

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

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

Vital Signs: As with other antipsychotics with α1 adrenergic blocking activity, quetiapine may induce postural hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose titration period (see WARNINGS AND PRECAUTIONS, Cardiovascular). In placebo-controlled clinical trials in schizophrenia, postural hypotension was reported with an incidence of 8% in quetiapine-treated patients compared to 2% in placebo-treated patients. Quetiapine 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.

Peripheral Edema: As with other antipsychotic agents, common cases (≥1% - <10%) of peripheral edema have been reported in patients treated with quetiapine.

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

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

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant quetiapine /placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week-placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for quetiapine compared to 0.6% (1/156) incidence for placebo. Quetiapine use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to quetiapine's potential for inducing orthostatic changes (see WARNINGS AND PRECAUTIONS, Cardiovascular). In bipolar disorder - mania trials the proportion of patients meeting the criteria for tachycardia was 0.5% (1/192) for quetiapine compared to 0% (0/178) for placebo.

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

Table 2 Treatment-Emergent Extrapyramidal Symptoms, Assessed by Spontaneous Reports, Simpson Scale, And Incidence of Anticholinergic Use

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

*Patients may have had more than one Parkinsonism adverse event

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

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

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

Dysphagia: There have been uncommon cases of dysphagia in patients administered quetiapine.

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

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

Abnormal Hematologic and Clinical Chemistry Findings
As with other antipsychotics, common cases of leucopenia and/or neutropenia have been observed in patients administered quetiapine. Uncommon cases of eosinophilia have been observed.

In all placebo-controlled monotherapy clinical trials among patients with a baseline neutrophil count $\geq 1.5 \times 10^9$ /L, the incidence of at least one occurrence of neutrophil count $<1.5 \times 10^9$ /L was 1.72% in patients treated with quetiapine, compared to 0.73% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count $<1.0 \times 10^9$/L, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9$/L, the incidence of at least one occurrence of neutrophil count $<0.5 \times 10^9$/L was 0.21% in patients treated with quetiapine and 0% in placebo treated patients and the incidence ≥ 0.5 - $<1.0 \times 10^9$/L was 0.75% in patients treated with quetiapine and 0.11% in placebo-treated patients. (See WARNINGS AND PRECAUTIONS, Hematologic).

Asymptomatic elevations in serum transaminases (AST, ALT) or gamma-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment (see WARNINGS AND PRECAUTIONS, Hepatic).

Quetiapine treatment was associated with small dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first 2 to 4 weeks of quetiapine treatment, with no further reduction during long-term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment (see WARNINGS AND PRECAUTIONS, Endocrine and Metabolism). Smaller decreases in total T_3 and reverse T_3 were seen only at higher doses. Levels of TBG were unchanged and in general reciprocal increases in TSH were not observed and there was no indication that quetiapine causes clinically relevant hypothyroidism.

Hyperglycaemia: Blood glucose increases to hyperglycaemic 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.

In 2 long-term bipolar maintenance placebo-controlled adjunct clinical trials, mean exposure 213 days for quetiapine (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 (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) 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 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) and elevations in total cholesterol (predominantly LDL cholesterol) (≥6.2064 mmol/L on at least one occasion) have been observed during treatment with quetiapine in clinical trials (see WARNINGS AND PRECAUTIONS, Cardiovascular). Lipid increases 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, which was driven by increases in LDL cholesterol. The mean LDL level increased at Week 24 by 10% in patients administered quetiapine, which was statistically significant. The total cholesterol/HDL ratio did not change significantly during therapy with quetiapine. Furthermore, triglycerides did not increase significantly nor did HDL cholesterol decrease during therapy. (See WARNINGS AND PRECAUTIONS, Cardiovascular).

Post-Market Adverse Drug Reactions

During post-marketing experience, leucopenia and/or neutropenia have been reported during quetiapine treatment. Resolution of leucopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leucopenia and/or neutropenia. (See WARNINGS AND PRECAUTIONS, Hematologic).

As with some other antipsychotics, hyperglycaemia 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, sometimes in patients with no reported history of hyperglycaemia. (See 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 treatment. The reporting rate of anaphylaxis associated with quetiapine 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 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.

DRUG INTERACTIONS

Drug-Drug Interactions

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

The Effect of Quetiapine on Other Drugs

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

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

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

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

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

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

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

The Effect of Other Drugs on Quetiapine

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

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

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

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

Divalproex: Co-administration of quetiapine (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 following coadministration with cimetidine, (a non-specific P450 enzyme inhibitor), no clinically significant interaction was observed.

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

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

Drug-Food Interactions
Quetiapine can be administered with or without food.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
Schizophrenia:
The usual starting dose of AVA-QUETIAPINE (quetiapine) is 25 mg b.i.d., titrated with increments of 25-50 mg b.i.d. per day, as tolerated, to a target dose of 300 mg/day given b.i.d. within four to seven days.

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

AVA-QUETIAPINE can be administered with or without food (see ACTIONS AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Clinical trials suggest that the usual effective treatment dose will be in the range of 300-600 mg/day (see Part II: CLINICAL TRIALS). However, some patients may require as little as 150 mg/day. 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 has not been associated with treatment-emergent EPS across the clinical dose range.

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

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

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

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

Dosing Considerations in Special Populations
Elderly: In clinical trials, 38 patients with schizophrenia or related disorders, 65 years of age or over, were treated with quetiapine (see WARNINGS AND PRECAUTIONS, Special Populations). Given the limited experience with quetiapine in the elderly, and the higher incidence of concomitant illness and concomitant medication in this population, AVA-QUETIAPINE 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. The rate of dose titration may thus need to be slower, and the daily therapeutic target dose lower, than that used in younger patients.

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

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

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

OVERDOSAGE

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 overdose. The lowest reported dose associated with coma has been in a patient who took 5,000 mg and had a full recovery within 3 days. The lowest reported dose associated with a death was in a patient who took 6,000 mg.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see WARNINGS AND PRECAUTIONS, Cardiovascular, Hypotension and Syncope).

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

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.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action and Pharmacodynamics
Quetiapine, a dibenzothiazepine derivative, is an antipsychotic agent. Quetiapine and the active plasma metabolite, N-desalkyl quetiapine interact with a broad range of neurotransmitter receptors. The extent to which the N-desalkyl quetiapine metabolite contributes to the pharmacological activity of quetiapine is not known.

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. 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.

N-desalkyl quetiapine: N-desalkyl quetiapine, similar to quetiapine, exhibits affinity for brain serotonin 5HT2 and dopamine D1 and D2 receptors. Additionally, like quetiapine, N-desalkyl quetiapine has high affinity at serotonin 5HT1 receptors, and histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors.

Pharmacokinetics
The pharmacokinetics of quetiapine and N-desalkyl quetiapine are linear within the clinical dose range. The kinetics of quetiapine are similar in men and women, and smokers and nonsmokers.

Absorption: Quetiapine is well absorbed following oral administration. In studies with radiolabelled drug, approximately 73% of the total radioactivity is recovered in the urine and 21% in the faeces over a period of one week. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively. Peak plasma concentrations of quetiapine generally occur within 2 hours after oral administration. Steady-state peak molar concentrations of the active metabolite N-desalkyl quetiapine are 35% of that observed for quetiapine.

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

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

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

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

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

Quetiapine and several of its metabolites (including N-desalkyl quetiapine) 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.

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 WARNINGS AND PRECAUTIONS, Special Populations and 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 resulted in a 40% increase in both AUC and C_{max}. Clearance of the drug decreased by 25% whereas $t_{½}$ was elevated by nearly 45%. Therefore, quetiapine should be used with caution in patients with mild hepatic impairment, especially during the initial dosing period. No pharmacokinetic data are available for any dose of quetiapine in patients with moderate or severe hepatic impairment (see WARNINGS AND PRECAUTIONS, Hepatic and DOSAGE AND ADMINISTRATION).

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

STORAGE AND STABILITY

AVA-QUETIAPINE should be stored at controlled room temperature 15 - 30°C (59-86°F).

DOSAGE FORMS, COMPOSITION AND PACKAGING

AVA-QUETIAPINE Tablets 25 mg: Each peach, round, biconvex, film-coated tablet, engraved "APO" on one side, "QUE" over "25" on the other side contains 25 mg quetiapine as quetiapine fumarate. Available in bottles of 100 tablets.

AVA-QUETIAPINE Tablets 100 mg: Each yellow, round, biconvex, film-coated tablet, engraved "APO" on one side, "QUE" over "100" on the other side contains 100 mg quetiapine as quetiapine fumarate. Available in bottles of 100 tablets.

AVA-QUETIAPINE Tablets 200 mg: Each white, round, biconvex, film-coated tablet, engraved "APO" on one side, "QUE" over "200" on the other side contains 200 mg quetiapine as quetiapine fumarate. Available in bottles of 100 tablets.

In addition to quetiapine fumarate, each tablet contains the excipients colloidal silicon dioxide, croscarmellose sodium, ethylcellulose 7FP, fumaric acid, hydroxypropyl cellulose type LF, hydroxypropyl methylcellulose 2910 E5, magnesium stearate, polyethylene glycol 8000, red ferric oxide (25 mg only), titanium dioxide, yellow ferric oxide (25 mg and 100 mg only).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Quetiapine Fumarate

Chemical Name:

1) Ethanol, 2-[2-(4-dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy] -, (E)-2-butenedioate (2:1)

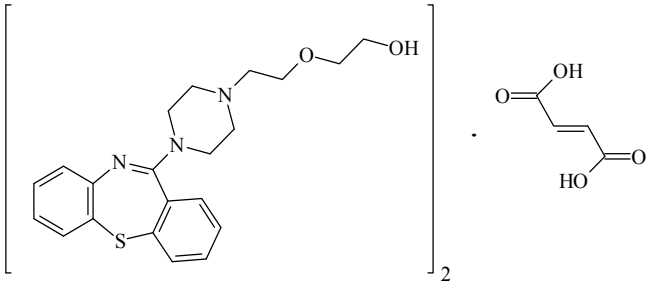
2) 2-[2-(4-Dibenzo[*b,f*][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]ethanol fumarate (2:1)

Molecular formula and molecular weight:

Quetiapine: $C_{21}H_{25}N_3O_2S$, 383.51

Quetiapine fumarate: $(C_{21}H_{25}N_3O_2S)_2 \cdot C_4H_4O_4$, 883.09

Structural Formula:



Physicochemical properties: A white to off-white crystalline powder

pKa: Quetiapine: pK_{a1} 3.3; pK_{a2} 6.8
Fumaric Acid: pK_{a1} 3.03; pH_{a2} 4.54

Partition Coefficient: Log P = 0.45 (Octanol/Water)

Melting point: Quetiapine fumarate: 172-173°C (Crystals from ethanol).

CLINICAL TRIALS

Comparative Bioavailability Studies

A randomized, single-dose, double-blinded, two-way crossover comparative bioavailability study, conducted under fasting conditions, was performed on healthy male and female volunteers. The rate and extent of absorption of quetiapine was measured and compared following a single oral dose (1 x 25 mg) of AVA-QUETIAPINE (quetiapine fumarate) or SEROQUEL® tablets. The results from measured data from a total of 31 volunteers (20 males and 11 females) are summarized in the following table.

Summary Table of the Comparative Bioavailability Data
Quetiapine Fumarate
(A single 25 mg dose: 1 x 25 mg tablet)
From Measured Data/Fasting Conditions
Geometric Least Square Mean
Arithmetic Mean (CV%)

Parameter	Ava–Quetiapine	Seroquel®†	Ratio of Geometric Means (%)##	90% Confidence Interval (%)##
AUCt (ng•h/mL)	269.493 294.185 (45)	290.868 318.362 (44)	92.7	87.4 – 98.2
AUCinf (ng•h/mL)	277.579 303.928 (46)	299.448 328.762 (44)	92.7	87.4 – 98.3
Cmax (ng/mL)	79.706 90.184 (53)	83.735 90.515 (38)	95.2	84.5 – 107.2
Tmax# (h)	0.99 (59)	1.28 (79)		
Thalf# (h)	5.26 (23)	5.12 (19)		

Arithmetic means (CV%) only.

Based on the least squares estimate.

† Seroquel® is manufactured by AstraZeneca Canada Inc., Canada, and was purchased in Canada.

Other Studies

Schizophrenia

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

1. In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of quetiapine (75, 150, 300, 600 and 750 mg/day on a t.i.d. schedule), the 4 highest doses of quetiapine

were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 were generally indistinguishable. Quetiapine, at a dose of 300 mg/day, was superior to placebo on the SANS.

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

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

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

Bipolar Disorder – Mania

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

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

In the two 12-week trials comparing quetiapine to placebo, quetiapine was significantly superior to placebo in reducing manic symptoms. Of those patients with a clinical response, 87% received doses of quetiapine between 400 and 800 mg per day; in the two individual studies, 52% and 81% of responders received doses between 600 and 800 mg per day (b.i.d. dosing).

DETAILED PHARMACOLOGY

Quetiapine is a multiple receptor antagonist. It exhibits affinity for brain serotonin $5HT_{1A}$ and $5HT_2$ receptors (IC_{50s}=717 and 148 nM, respectively), and dopamine D_1 and D_2 receptors (IC_{50s}=1268 and 329 nM, respectively). Quetiapine has lower affinity for dopamine D_2 receptors, than serotonin $5HT_2$ receptors. Quetiapine also has high affinity at histamine H_1 receptors (IC_{50}=30 nM) and adrenergic α_1 receptors (IC_{50}=94 nM), with a lower affinity at adrenergic α_2 receptors (IC_{50}=271 nM), but no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM). N-desalkyl quetiapine is an active human plasma metabolite. Similar to quetiapine, it exhibits affinity for brain serotonin $5HT_2$ and dopamine D_1 and D_2 receptors. Additionally, N-desalkyl quetiapine has high affinity at serotonin $5HT_1$ receptors, and histaminergic and adrenergic α_1 receptors, with a lower affinity at adrenergic α_2 receptors.

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

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

Pharmacology of Metabolites

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

TOXICOLOGY

Thyroid

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

Cataracts

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

Acute Toxicity

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

Subacute/Chronic Toxicity

In multiple dose studies in rats, dogs and monkeys (refer to Table 3 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).

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

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

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

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

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

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

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

Carcinogenicity
Results from the 2 year carcinogenicity studies performed in mice and rats (and mouse sighting studies) are summarized in Table 4.

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 hyperprolactinaemia.

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.

Table 3 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 hyperprolactinaemia 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 50 100	Decreased motor activity, ataxia, somnolence, miosis, increased heart rate and hypothermia were observed for animals in all compound-treated groups. In general the incidence was dose-related and decreased with time. All effects reversed on withdrawal.
Dog Beagle	oral tablets	6 months dosing and 8 weeks withdrawal	3 or 4	0 25 50 100	Up to 8 weeks transient sedation and increased heart rate. Dose-related decreases in body weight gain. At 100 mg/kg/day 13-26% decrease in plasma cholesterol and prominent posterior Y sutures, swelling of lens fiber tips and 3/8 females with cataracts; 1 epileptiform seizure, 4/8 muscular twitching. 50 mg/kg/day was the no adverse-effect dose level.

Table 3 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 weeks withdrawal	4	0, rising dose for 4 weeks then 25, 100 and 225 mg/kg/day administered as 3 doses/day	Dose-related incidence and severity of behavioural changes. No abnormal signs on drug withdrawal. 40-60% reduction in plasma cholesterol at 225 mg/kg/day with delta-8-cholestanol present at 15% of cholesterol level at 100 and 225 mg/kg/day. No lens opacities. Minor lens changes at all doses with no lens pathology. Transient elevation of prolactin and mild mammary gland hyperplasia (in males) and T_3 levels reduced and mild thyroid follicular cell hypertrophy at 100 and 250 mg/kg/day. Red cell indices reduced and liver enlargement with hepatocyte hypertrophy and fat deposition at 250 mg/kg/day.

Table 4 Carcinogenicity (And Mouse Sighting) Studies With Quetiapine

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

Reproduction and Teratology
Results from the individual reproduction and teratology studies, performed with quetiapine in rats and rabbits, are summarized in Table 5.

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.

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).

Table 5 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 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 Segment II Teratology	Oral	21 days females dosed from d6 to d15 gestation	F_o generation: 13 F/group	0, 25, 50, 200	Adverse clinical signs at all dose levels. No effect on reproductive function of the dams or development of fetuses, behaviour or reproductive function of the offspring at any dose level.
Rabbit Dutch Belted Segment II Teratology	Oral	28 days females dosed d6 to d18 gestation	F_o generation: 20 F 20 F 20 F 20 F	0 25 50 100	Reduced weight gain and adverse clinical signs at all doses. No effects on fetal survival. Fetal weight reduced at 100 mg/kg/day. No major fetal abnormalities. Specific skeletal anomalies present associated with reduced fetal weight at 100 mg/kg/day.

Table 5 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 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)

REFERENCES

1) Arvanitis LA, Miller BG, Seroquel Trial 13 Study Group. Multiple fixed doses of 'Seroquel' (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. Biol Psychiatry 1997;42:233-46.

2) Borison RL, Arvanitis LA, Miller BG, Study-Group. ICI 204,636, an atypical antipsychotic: efficacy and safety in a multicenter, placebo-controlled trial in patients with schizophrenia. J Clin Psychopharmacol 1996;16(2):158-69.

3) Casey DE. 'Seroquel' (quetiapine): preclinical and clinical findings of a new atypical antipsychotic. Exp Opin Invest Drugs 1996;5(8):939-57.

4) Emsley RA, Raniwalla J, Bailey PJ, Jones AM. A comparison of the effects of quetiapine ('Seroquel') and haloperidol in schizophrenic patients with a history of and a demonstrated partial response to conventional antipsychotic treatment. International Clinical Pharmacology 2000; 15(3):121-31.

5) Fabre LF, Arvanitis L, Pultz J, Jones VM, Malick JB, Slotnick VB. ICI 204,636, a novel atypical antipsychotic: early indication of safety and efficacy in patients with chronic and subchronic schizophrenia. Clin Ther 1995;17(3):366-78.

6) Goldstein JM, Litwin LC, Sutton EB and Malick JB. Seroquel: electrophysiological profile of a potential atypical antipsychotic. Psychopharmacology 1993;112(2-3):293-8.

7) Hamner MB, Arvanitis LA, Miller BG, Link CGG, Hong WW. Plasma prolactin in schizophrenia subjects treated with SeroquelTM (ICI 204,636). Psychopharmacology Bull 1996;32(1):107-10.

8) Migler BM, Warawa EJ and Malick JB. Seroquel: behavioural effects in conventional and novel tests for atypical antipsychotic drug. Psychopharmacology 1993;112(2-3):299-307.

9) Peuskens J, Link CGG. A comparison of quetiapine and chlorpromazine in the treatment of schizophrenia. Acta Psychiatr Scand 1997;96:265-73.

10) Pinninti NR, Mago R, Townsend J, Doghramji K. Periodic restless legs syndrome associated with quetiapine use: a case report. J Clin Psychopharmacol. 2005 Dec;25(6):617-8.

11) Pullen RH, Palermo KM and Curtis MA. Determination of an antipsychotic agent (ICI 204,636) and its 7-hydroxy metabolite in human plasma by high-performance liquid chromatography and gas chromatography-mass spectrometry. J Chromatogr Biomed Appl 1992;573(1):49-57.

12) Saller CF, Salama AI. Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology 1993;112(2-3):285-92.

13) Small JG, Hirsch SR, Arvanitis LA, Miller BG, Link CG. Quetiapine in patients with schizophrenia. A high- and low-dose double-blind comparison with placebo. Arch Gen Psychiatry 1997;54:549-57.

14) Swerdlow NR, Zisook D, Taaid N. Seroquel (ICI 204,636) restores prepulse inhibition of acoustic startle in apomorphine-treated rats: similarities to clozapine. Psychopharmacology 1994;114(4):675-8.

15) Wetzel H, Szegedi A, Hain C, Weisner J, Schlegel S and Benkert O. Seroquel (ICI 204,636), putative "atypical" antipsychotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changes of neuroendocrinological and EEG parameters. Psychopharmacology 1995;119(2):231-8.

16) Product Monograph –SEROQUEL® (quetiapine fumarate) tablets, AstraZeneca Canada Inc., Date of Revision: May 21, 2008 Control No.: 120108.

PART III: CONSUMER INFORMATION

[Pr]AVA-QUETIAPINE
Quetiapine Fumarate

This leaflet is part III of a three-part "Product Monograph" published when AVA-QUETIAPINE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about AVA-QUETIAPINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
AVA-QUETIAPINE (quetiapine fumarate) is used to:

- treat the symptoms of schizophrenia, such as hallucinations (hearing or seeing things which are not there), fixed false beliefs, unusual suspiciousness, or emotional withdrawal. Patients may also feel depressed, anxious or tense.
- treat the symptoms of mania associated with bipolar disorder, such as aggressiveness, agitation, impulsive behaviour or excessively elevated mood.

Your doctor may have prescribed AVA-QUETIAPINE for another reason. Ask your doctor if you have any questions about why AVA-QUETIAPINE has been prescribed for you.

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

What it does:
AVA-QUETIAPINE is a medication that belongs to a class of medicines called "atypical antipsychotics".

Illnesses that affect the brain, such as schizophrenia and bipolar disorder, may be due to certain chemicals in the brain being out of balance. These imbalances may cause some of the symptoms you may be experiencing. Doctors and scientists are not sure what causes these imbalances to occur. AVA-QUETIAPINE is thought to work by regulating the imbalance of chemicals in the brain.

When it should not be used:
Do not take AVA-QUETIAPINE if you have had an allergic reaction to AVA-QUETIAPINE or any of the ingredients listed in the "nonmedicinal ingredients" section of this leaflet.

What the medicinal ingredient is:
Quetiapine Fumarate

What the important nonmedicinal ingredients are:
AVA-QUETIAPINE tablets contain the following nonmedicinal ingredients: colloidal silicon dioxide, croscarmellose sodium, ethylcellulose 7FP, fumaric acid, hydroxypropyl cellulose type LF, hydroxypropyl methylcellulose 2910 E5, magnesium stearate, polyethylene glycol 8000, red ferric oxide (25 mg only), titanium dioxide, yellow ferric oxide (25 mg and 100 mg only).

What dosage forms it comes in:
Tablets – 25 mg, 100 mg, and 200 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Studies with various medications of the group to which AVA-QUETIAPINE belongs, including AVA-QUETIAPINE, when used in elderly patients with dementia have been associated with an increased rate of death. AVA-QUETIAPINE is not indicated in elderly patients with dementia.

Before starting AVA-QUETIAPINE, be sure to tell your doctor:

- if you have had an allergic reaction to any medicine which you have taken previously to treat your condition, or if you think you might be sensitive or allergic to any of the ingredients in AVA-QUETIAPINE.
- about any other medications - prescription, non-prescription or alternative - that you are taking or plan to take. Certain medications can seriously affect the way other medications work.
- if you are pregnant or plan to become pregnant while taking AVA-QUETIAPINE.
- if you are breast-feeding or are planning on breast-feeding while taking AVA-QUETIAPINE. You should not breast-feed while taking AVA-QUETIAPINE.
- if you drink alcohol or use street drugs.
- if you have any health problems.
- if you have any heart problems and/or low blood pressure or have had a stroke.
- if you have a history of seizures.
- if you have diabetes, a family history of diabetes or high blood sugar during pregnancy.
- if you have a history of liver or kidney problems.
- if you know that you had a low white blood cell count in the past which may or may not have been caused by other medicines.
- if you exercise vigorously or work in hot or sunny places.

If you already have diabetes, you should be monitored for worsening of your diabetes.

Do not drive or operate machinery until you know your response to this medication, as AVA-QUETIAPINE can cause drowsiness.

INTERACTIONS WITH THIS MEDICATION

Because certain medications can seriously affect the way other medications work, it is important to tell all doctors, dentists, and pharmacists who are treating you that you are taking AVA-QUETIAPINE. As well, be sure to tell them about any other medications – prescription, non-prescription or alternative – that you are taking or plan to take.

You should not drink alcohol while taking AVA-QUETIAPINE, as the combination could increase the effects of the alcohol.

You should tell your doctor if you are taking or about to stop taking medications for anxiety, or depression or to help you sleep.

Dopamine agonists, e.g. levodopa (antiparkinsonian agent), may decrease the effect of AVA-QUETIAPINE.

Medications known to interact with AVA-QUETIAPINE include carbamazepine (anticonvulsant), phenytoin (anticonvulsant), ketoconazole (antifungal), and protease inhibitors (for treating Human Immunodeficiency Virus).

You should tell your doctor if you are taking erythromycin (antibiotic), clarithromycin (antibiotic), diltiazem, verapamil, nefazodone, thioridazine (antipsychotic), or blood pressure medications.

PROPER USE OF THIS MEDICATION

AVA-QUETIAPINE is not recommended for use in patients under 18 years old.

Usual adult dose:
In order for AVA-QUETIAPINE to help you feel better, it is very important to take it every day exactly as your doctor tells you to. Take the exact number of tablets your doctor has prescribed at the right time every day.

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

If you stop taking AVA-QUETIAPINE abruptly you may experience withdrawal symptoms such as insomnia (inability to sleep), nausea, and vomiting.

To make sure you are getting the most benefit from AVA-QUETIAPINE, you must:

- Continue taking AVA-QUETIAPINE everyday and
- Keep your doctor well informed of how you are feeling, both good and bad.

By doing these two things, you and your doctor together will be able to make sure that you are getting the best dose of AVA-QUETIAPINE for you.

You may take AVA-QUETIAPINE with or without food.

Do not give AVA-QUETIAPINE to anyone else. Your doctor has prescribed AVA-QUETIAPINE for you only.

Overdose:
In case of AVA-QUETIAPINE overdose or if you think you, or anyone else, are experiencing severe episodes of any of the side effects of AVA-QUETIAPINE (especially drowsiness, including also rapid heart beat, lightheadedness and/or dizziness, especially when standing up quickly or getting out of bed), call your doctor or poison control centre or go to the nearest hospital emergency room right away. Make sure to bring your medication bottle with you.

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

Here are some tips that can help you remember to take each dose of AVA-QUETIAPINE:

- Take your AVA-QUETIAPINE at the same time every day;
- Take AVA-QUETIAPINE during daily events which will help you remember to take your medicine as well, e.g., mealtime or bedtime;
- Use a pill container that will separate your AVA-QUETIAPINE doses by the day of the week;
- Use a calendar to note the day and time after you have taken each dose to help you keep track of when you need to take your AVA-QUETIAPINE;
- Keep a written reminder to take your AVA-QUETIAPINE that can be easily seen, e.g., on a mirror or on the refrigerator;
- Have a family member or friend remind you to take your medication.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like any medication, AVA-QUETIAPINE may produce side effects in some people.

Increases in blood glucose (sugar) and hyperglycaemia (high blood sugar) have been observed with AVA-QUETIAPINE. Also, occasional cases of diabetes have been reported.

Light-headedness and dizziness (symptoms of postural hypotension) and drowsiness are among the most common side effects you may experience while taking AVA-QUETIAPINE, particularly during the first week of treatment or after an increase in dose. The dizziness and drowsiness are usually mild and should go away with time. To help prevent these feelings, be careful to move slowly when you are getting up from a sitting or lying position.

Discontinuation symptoms which occur upon stopping AVA-QUETIAPINE have been reported very commonly and include insomnia (inability to sleep), nausea, headache, diarrhea, vomiting, dizziness, and irritability. These symptoms usually go away after 1 week from your last dose.

Other common side effects may include: headache, rapid heart beat, constipation, indigestion, dry mouth, feeling weak, swelling of arms and legs, fainting, stuffy nose, upset stomach or abdominal pain, blurred vision, some weight gain, and changes in laboratory tests for liver and thyroid functions.

As feelings of drowsiness are also common at the start of treatment, or when your dose is increased, if you have to drive, operate machinery or do anything else that requires you to be fully alert, use extra caution until you are sure AVA-QUETIAPINE does not cause you to be drowsy.

There have been uncommon cases of difficulty swallowing and disturbance in speech and language.

There have also been reports, in a small number of patients, of changes to the lens of the eye. Although it is not known whether or not these changes are caused by AVA-QUETIAPINE, your doctor may advise you that a specific type of eye exam is recommended in order to maximize safe use of this drug.

In very rare cases, this type of medicine can interfere with your body's ability to control body temperature. Therefore, take care to avoid becoming overheated or dehydrated (for example with vigorous exercise, or exposure to extreme heat) while taking AVA-QUETIAPINE.

The following may also occur with AVA-QUETIAPINE, and may be seen in routine blood testing:

- Decrease in the amount of white blood cells. These changes will normally disappear when stopping the treatment of AVA-QUETIAPINE.
- Increase in one type of white blood cells (eosinophilia) which is sometimes seen in allergic reactions.
- Increase in the amount of liver enzymes. These changes will normally disappear when continuing the treatment of AVA-QUETIAPINE.
- Increase in the amount of fatty substances (lipid levels, such as triglycerides and cholesterol) in the blood.
- Increase in the amount of 'creatine phosphokinase', a substance in the muscles.
- Increase in the amount of sugar (glucose) in the blood.

One of the most important things for you to do to minimize the risks from side effects, while helping AVA-QUETIAPINE work for you, is to contact your doctor or pharmacist if you notice any symptom that worries you, even if you think it is not connected with this medicine or is not listed here.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor right away		Stop taking drug and call your doctor or pharmacist right away
		Only if severe	In all cases	
Uncommon	Symptoms of allergic reactions such as, skin lumps, bumps or swelling			√
	Restless legs (unpleasant sensations in the legs)		√	
	Seizure (i.e. loss of consciousness with uncontrollable shaking "fit")			√
Rare	Long-lasting and painful erection)		√	
	Fever, muscle stiffness, marked increase in blood pressure and/or heartbeats, and reduced consciousness		√	
	Muscle twitching or abnormal movements of your face and tongue		√	
Very rare	Anaphylaxis (severe form of allergic reaction; may include severe difficulty breathing and shock)			√

This is not a complete list of side effects. For any unexpected effects while taking AVA-QUETIAPINE, contact your doctor or pharmacist.

HOW TO STORE IT

Store at controlled room temperature 15-30°C (59-86°F) and well out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
    - Fax toll-free to 1-866-678-6789, or
    - Mail to:
      Canada Vigilance Program
      Health Canada
      Postal Locator 0701D
      Ottawa, Ontario
      K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your doctor, pharmacist or other healthcare professional.

This leaflet plus the full product monograph, prepared for health professionals, can be obtained by contacting AVANSTRA INC. at:

Telephone: 1-855-708-3678
Email: medinfo@avanstra.com

This leaflet was prepared by Avanstra Inc., Toronto, ON, M9L 1T9.

Last revised: February 16, 2011