PRODUCT MONOGRAPH

Pr SEROQUEL®

(quetiapine fumarate tablets)

quetiapine 25, 100, 150, 200 and 300 mg

Antipsychotic Agent

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THERAPEUTIC CLASSIFICATION

Antipsychotic Agent

ACTIONS AND CLINICAL PHARMACOLOGY

SEROQUEL (quetiapine), a dibenzothiazepine derivative, is an antipsychotic agent which interacts with a broad range of neurotransmitters. Quetiapine exhibits affinity for brain serotonin $5HT_2$ and $5HT_{1A}$ receptors (*in vitro*, Ki = 288 and 557 nM, respectively), and dopamine D_1 and D_2 receptors (*in vitro*, Ki = 558 and 531 nM, respectively). It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2 receptors which is believed to contribute to the antipsychotic properties and low extrapyramidal symptoms (EPS) liability of SEROQUEL. Quetiapine also has high affinity for histamine H_1 receptors (*in vitro*, Ki = 10 nM) and adrenergic α_1 receptors (*in vitro*, Ki = 13 nM), with a lower affinity for adrenergic α_2 receptors (*in vitro*, Ki = 782 nM), but no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors.

Pharmacokinetics

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

Absorption

Quetiapine is well absorbed following oral administration. In studies with radiolabelled drug, approximately 73% of the total radioactivity is recovered in the urine and 21% in the faeces over a period of one week. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively. Peak plasma concentrations of quetiapine generally occur within 2 hours after oral administration.

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. 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.

Quetiapine and several of its metabolites were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities, but only at concentrations at least 10 to 50 fold higher than those observed at the 300 mg/day recommended daily dose in humans.

Special Populations

Elderly

The mean clearance of quetiapine in the elderly is approximately 30 to 50% of that seen in adults aged 18-65 years (see PRECAUTIONS, 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 PRECAUTIONS, 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 SEROQUEL 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,

SEROQUEL 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 SEROQUEL in patients with moderate or severe hepatic impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Clinical Trials

Efficacy

Schizophrenia

The efficacy of SEROQUEL 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 SEROQUEL (75, 150, 300, 600 and 750 mg/day on a t.i.d. schedule), the 4 highest doses of SEROQUEL 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. SEROQUEL, 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 SEROQUEL 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 SEROQUEL 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 SEROQUEL (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.) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Clinical trials have demonstrated that SEROQUEL 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 SEROQUEL 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 SEROQUEL to placebo, SEROQUEL was significantly superior to placebo in reducing manic symptoms. Of those patients with a clinical response, 87% received doses of SEROQUEL 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).

INDICATIONS AND CLINICAL USE

Schizophrenia

SEROQUEL (quetiapine) is indicated for the management of the manifestations of schizophrenia. The antipsychotic efficacy of SEROQUEL was established in short-term (6-week) controlled inpatient trials (see ACTIONS and CLINICAL PHARMACOLOGY). The efficacy of SEROQUEL 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

SEROQUEL is indicated as monotherapy for the acute management of manic episodes associated with bipolar disorder.

The efficacy of SEROQUEL in bipolar disorder - mania was established in two 12-week clinical trials of bipolar patients (See ACTIONS AND CLINICAL PHARMACOLOGY). The safety and effectiveness of SEROQUEL for long-term use, and for prophylactic use in bipolar disorder has not been evaluated.

Geriatrics (> 65 years of age): SEROQUEL is not indicated in elderly patients with dementia. See WARNINGS, Serious Warnings Box and PRECAUTIONS, Use in the Elderly – Use in Geriatric Patients with Dementia.

CONTRAINDICATIONS

SEROQUEL (quetiapine) is contraindicated in patients with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Serious Warnings

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 PRECAUTIONS, Use in the Elderly - Use in Geriatric Patients with Dementia).

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome is a potentially fatal symptom complex that has been reported in association with antipsychotic drugs, including SEROQUEL (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 SEROQUEL, 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)

A syndrome of potentially irreversible, involuntary, dyskinetic movements 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 controlled clinical trials with SEROQUEL, the incidence of EPS was not statistically significantly different than placebo across the recommended therapeutic dose range. This may predict that SEROQUEL has less potential than standard antipsychotic agents to induce TD.

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, SEROQUEL 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 SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

PRECAUTIONS

Hyperglycaemia

As with some other antipsychotics, exacerbation of pre-existing diabetes, hyperglycaemia, diabetic ketoacidosis, and diabetic coma including some fatal cases have been reported very rarely (<0.01%) during the use of SEROQUEL, sometimes in patients with no reported history of hyperglycaemia (see ADVERSE REACTIONS, Post-Market Experience).

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 hyperglycaemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycaemia-related adverse events in patients treated with atypical antipsychotics are not available.

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 anti-diabetic 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.

Hypotension and Syncope

As with other drugs that have high α_1 adrenergic receptor blocking activity, SEROQUEL (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 SEROQUEL, 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). SEROQUEL 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).

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 SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. The possibility of lenticular changes during long-term use of SEROQUEL 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 SEROQUEL and at 6 month intervals thereafter, are recommended. If clinically significant lens changes associated with SEROQUEL use are observed, discontinuation of SEROQUEL should be considered.

Seizures

In controlled schizophrenia clinical trials, there was no difference in the incidence of seizures in patients treated with SEROQUEL or placebo (incidence of 0.4% or 3 events per 100 patient years in patients given SEROQUEL, 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.

Hypothyroidism

Clinical trials in schizophrenia demonstrated that SEROQUEL is associated with a dose-related decrease in total and free thyroxine (T_4). On average SEROQUEL was associated with about a 20% mean reduction in thyroxine levels (both total and free). Forty-two percent of SEROQUEL-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 SEROQUEL. These reductions were maintained without adaption 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 SEROQUEL (schizophrenia and bipolar studies combined) experienced persistent increases in TSH, and 0.25% of patients were treated with thyroid replacement.

Cholesterol and Triglyceride Elevations

In short-term placebo-controlled schizophrenia trials, SEROQUEL-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. There was little relation between these changes and weight changes observed during the trial.

Hepatic Impairment

Decreased clearance of SEROQUEL was observed in patients with mild hepatic impairment (see ACTIONS and CLINICAL PHARMACOLOGY). 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 SEROQUEL in patients with moderate or severe hepatic impairment. However, should clinical judgement deem treatment with SEROQUEL necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see ACTIONS AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

Transaminase Elevations

During premarketing clinical trials, therapy with SEROQUEL was associated with elevation of hepatic transaminases, primarily ALT (SGPT). Within a clinical trial database of 1892 SEROQUEL-treated schizophrenia patients, with baseline ALT (SGPT) levels <60 IU/L, 5.3% (101/1892) had treatment-emergent ALT (SGPT) 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 SEROQUEL-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 SEROQUEL therapy. Of the 101 SEROQUEL-treated patients whose enzyme levels increased to >120 IU/L, 40 discontinued treatment while their ALT (SGPT) values were still raised. In 114 SEROQUEL-treated patients whose baseline ALT (SGPT) 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 SEROQUEL-treated and placebo-treated patients.

Precautions should be exercised when using SEROQUEL 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 SEROQUEL, 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 SEROQUEL therapy.

Hyperprolactinemia

Elevation of prolactin levels was not seen in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound. As is common with compounds which stimulate prolactin release, the administration of SEROQUEL 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 tumorigenesis. 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 SEROQUEL, across the recommended dose range, and placebo.

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 SEROQUEL 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 SEROQUEL was 2.8 kg.

Potential Effect on Cognitive and Motor Performance

Somnolence was a commonly reported adverse event in patients treated with SEROQUEL, especially during the initial dose titration period. Since SEROQUEL 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 SEROQUEL therapy does not affect them adversely.

Antiemetic Effect

Consistent with its dopamine antagonist effects, SEROQUEL 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 tumor or intestinal obstruction.

Body Temperature Regulation

Although not reported with SEROQUEL disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL 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.

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. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

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.

Drug Interactions

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

<u>The Effect of SEROQUEL on Other Drugs</u>
Alcohol: SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with psychotic disorders. Alcoholic beverages should be avoided while taking SEROQUEL.

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

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

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

Antipyrine: SEROQUEL did not induce the hepatic enzyme systems involved in the metabolism of anytipyrine.

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

Divalproex: Co-administration of SEROQUEL (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 SEROQUEL

Hepatic Enzyme Inducers: Concomitant use of SEROQUEL 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 SEROQUEL, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of SEROQUEL 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 SEROQUEL and another microsomal enzyme inducer, phenytoin, caused five-fold increases in the clearance of quetiapine. Increased doses of SEROQUEL may be required to maintain control of psychotic symptoms in patients co-administered SEROQUEL and phenytoin and other hepatic enzyme inducers (e.g, barbiturates, rifampicin, etc.).

The dose of SEROQUEL 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 SEROQUEL. 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 SEROQUEL should be reduced during concomitant use of quetiapine and potent CYP3A4 inhibitors (such as azole antifungals and macrolide antibiotics). 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 SEROQUEL (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 SEROQUEL 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 SEROQUEL (300 mg b.i.d.), increased the clearance of SEROQUEL 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 SEROQUEL.

Use in the Elderly

The number of patients 65 years of age or over, with schizophrenia or related disorders, exposed to SEROQUEL, 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 SEROQUEL in the elderly patient, (see DOSAGE AND ADMINISTRATION).

Use in Geriatric Patients with Dementia:
<u>Overall Mortality:</u> 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 SEROQUEL in this population, the incidence of mortality was 5.5% for SEROQUEL-treated patients compared to 3.2% for placebo-treated patients. SEROQUEL is not indicated in elderly patients with dementia.

Use in Children and Adolescents

The safety and efficacy of SEROQUEL in children under the age of 18 years have not been established.

Use in Patients with Renal Impairment

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

Use in Pregnancy

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

Use in Nursing Mothers

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 SEROQUEL.

ADVERSE REACTIONS

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

The 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.

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 SEROQUEL (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 (SGPT) levels.

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

Adverse Events Associated with Discontinuation

Short-Term Placebo-Controlled Clinical Trials:

Schizophrenia: Overall, 3.9% of SEROQUEL-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 SEROQUEL (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 SEROQUEL-treated patients, 5% discontinued due to an adverse event. Somnolence was the single most common adverse event leading to withdrawal of 24 patients from SEROQUEL, 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).

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 SEROQUEL (doses of 150 mg/day or more) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 1 Adverse Events Reported For At Least 1% Of Quetiapine-Treated Subjects (Doses ≥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 (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		
SGPT increased	7	2
SGOT 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.

Weight Gain: During acute therapy (up to 6 weeks) in placebo-controlled schizophrenia clinical trials, mean weight gain in patients taking SEROQUEL 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 PRECAUTIONS). In the acute placebo-controlled bipolar mania clinical trials (up to 12 weeks) mean weight gain in patients taking SEROQUEL 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 SEROQUEL was 2.8 kg.

Seizures: There have been occasional reports of seizures in patients administered SEROQUEL, although the frequency was no greater than that observed in patients administered placebo in controlled clinical trials (see PRECAUTIONS).

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

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

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

Vital Signs: As with other antipsychotics with α_1 adrenergic blocking activity, SEROQUEL may induce postural hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose titration period (see PRECAUTIONS). In placebo-controlled clinical trials in schizophrenia, postural hypotension was reported with an incidence of 8% in SEROQUEL-treated patients compared to 2% in placebo-treated patients. SEROQUEL 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.

Laboratory Changes: As with other anti-psychotics, leucopenia and/or neutropenia have been observed in patients administered SEROQUEL. Occasionally, eosinophilia has been observed.

There were no cases of persistent severe neutropenia or agranulocytosis reported in controlled clinical trials with SEROQUEL.

Asymptomatic elevations in serum transaminases [SGOT (AST), SGPT (ALT)] or γ-GT levels have been observed in some patients administered SEROQUEL. These elevations were usually reversible on continued SEROQUEL treatment (see PRECAUTIONS).

Small elevations in non-fasting serum triglyceride levels and total cholesterol have been observed during treatment with SEROQUEL (see PRECAUTIONS).

SEROQUEL 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 PRECAUTIONS). 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, with no indication that SEROQUEL causes clinically relevant hypothyroidism.

Peripheral Oedema: As with other antipsychotic agents, rare cases of peripheral oedema have been reported in patients treated with SEROQUEL.

Hypersensitivity: Very rarely, hypersensitivity including angioedema has been reported.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/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 SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL 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 SEROQUEL's potential for inducing orthostatic changes (see PRECAUTIONS). In bipolar disorder - mania trials the proportion of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL 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 SEROQUEL 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 SEROQUEL

	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 SEROQUEL 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 SEROQUEL, there were no differences between the SEROQUEL 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.

POST-MARKET EXPERIENCE

During post-marketing experience, leucopenia and/or neutropenia have been reported during SEROQUEL treatment. Resolution of leucopenia and/or neutropenia has followed cessation of therapy with SEROQUEL. Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leucopenia and/or neutropenia. As with some other antipsychotics, exacerbation of pre-existing diabetes, hyperglycaemia, diabetic ketoacidosis, and diabetic coma including some fatal cases have been reported very rarely (<0.01%) during the use of SEROQUEL, sometimes in patients with no reported history of hyperglycaemia. A causal relationship to SEROQUEL has not been established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Clinical Trials

In clinical trials, experience with SEROQUEL (quetiapine) in overdosage is limited. Estimated doses of up to 20 g of SEROQUEL have been taken, no fatalities were reported and patients recovered without sequelae.

Postmarketing

In postmarketing experience, there have been cases of coma and death in patients taking a SEROQUEL overdose. The lowest reported dose associated with coma has been in a patient

who took 5 g and had a full recovery within 3 days. The lowest reported dose associated with a death was in a patient who took 10.8 g.

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.

DOSAGE AND ADMINISTRATION

Schizophrenia

The usual starting dose of SEROQUEL (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 SEROQUEL 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.

SEROQUEL can be administered with or without food (see CLINICAL PHARMACOLOGY, Pharmacokinetics).

Clinical trials suggest that the usual effective treatment dose will be in the range of 300-600 mg/day (see CLINICAL PHARMACOLOGY, 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 SEROQUEL 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 ACTIONS and CLINICAL PHARMACOLOGY, 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.

Elderly

In clinical trials, 38 patients with schizophrenia or related disorders, 65 years of age or over, were treated with SEROQUEL (see PRECAUTIONS). Given the limited experience with SEROQUEL in the elderly, and the higher incidence of concomitant illness and concomitant medication in this population, SEROQUEL should be used with caution. The mean plasma clearance of SEROQUEL 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 PHARMACOLOGY). Therefore, SEROQUEL 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 tolerability in the individual patient. No pharmacokinetic data are available for any dose of SEROQUEL in patients with moderate to severe hepatic impairment. However, should clinical judgement deem treatment with SEROQUEL necessary, the drug should be used with great caution in patients with moderate or severe hepatic impairment (see PRECAUTIONS and ACTIONS AND CLINICAL PHARMACOLOGY).

Renal Impairment

As clinical experience is lacking, caution is advised (see PRECAUTIONS).

PHARMACEUTICAL INFORMATION

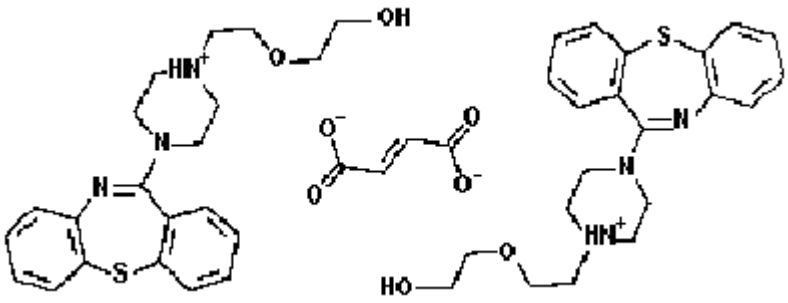
Drug Substance

Proper Name: quetiapine fumarate

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

Code Name: ICI 204,636 fumarate

Structural Formula:



Molecular Formula: $C_{42}H_{50}O_4N_6S_2 \cdot C_4H_4O_4$

Molecular Weight: 883.1

Ionization Constant: pKa_1 = 6.83 in phosphate buffer at 22°C
pKa_2 = 3.32 in formic buffer at 22°C

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

Melting Point: 172.0 - 174°C

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

Composition

SEROQUEL is available in 5 strengths containing 25, 100, 150, 200 or 300 mg quetiapine per tablet (as quetiapine fumarate). The core of the tablet contains the excipients povidone, calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate type A, lactose monohydrate and magnesium stearate. The coating of the tablet contains hydroxypropyl methylcellulose 2910, polyethylene glycol 400, titanium dioxide, yellow ferric oxide (25 mg, 100 mg and 150 mg tablets) and red ferric oxide (25 mg tablets).

Stability and Storage Recommendations

SEROQUEL should be stored between 15 - 30°C.

AVAILABILITY OF DOSAGE FORMS

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

25 mg quetiapine tablets are peach coloured, round, biconvex, intagliated with 'SEROQUEL' and '25' on one side and plain on the other, available in blister packages of 60 tablets and high-density polyethylene (HDPE) bottles of 100 tablets.

100 mg quetiapine tablets are yellow coloured, round, biconvex, intagliated with 'SEROQUEL' and '100' on one side and plain on the other, available in blister packages of 90 tablets and HDPE bottles of 100 tablets.

150 mg quetiapine tablets are pale yellow coloured, round, biconvex, intagliated with 'SEROQUEL' and '150' on one side and plain on the other, available in HDPE bottles of 100 tablets.

200 mg quetiapine tablets are white, round, biconvex, intagliated with 'SEROQUEL' and '200' on one side and plain on the other, available in blister packages of 90 tablets and HDPE bottles of 100 tablets.

300 mg quetiapine tablets are white, capsule-shaped, biconvex, intagliated with 'SEROQUEL' on one side and '300' on the other, available in HDPE bottles of 100 tablets.

INFORMATION FOR THE CONSUMER

Pr SEROQUEL®

(quetiapine fumarate tablets)

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

Before taking SEROQUEL, read this leaflet carefully. It contains general points about SEROQUEL and will add to the instructions you have received from your doctor. While reading it is not a substitute for talking with your doctor, the leaflet may answer some of the questions you have, and help you understand how to take your medication to get the most benefit from it. Talk to your doctor or pharmacist if you have concerns, or need information or advice about taking this medication. Keep this leaflet until you have taken all of your SEROQUEL tablets.

WHAT IS SEROQUEL USED FOR?

SEROQUEL (quetiapine fumarate) (pronounced SER-O-KWELL) is a medication that belongs to a class of medicines called "atypical antipsychotics". SEROQUEL is used to treat the symptoms of schizophrenia and mania associated with bipolar disorder. Schizophrenia symptoms include hallucinations (hearing or seeing things which are not there), fixed false beliefs, unusual suspiciousness, or emotional withdrawal. Patients suffering from schizophrenia may also feel depressed, anxious or tense. Symptoms of mania associated with bipolar disorder may include, aggressiveness, agitation, impulsive behaviour or excessively elevated mood. Your doctor may have prescribed SEROQUEL for another reason. Ask your doctor if you have any questions about why SEROQUEL has been prescribed for you.

HOW DOES SEROQUEL WORK?

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. SEROQUEL is thought to work by regulating the imbalance of chemicals in the brain.

SEROQUEL is not a cure for your condition but it can help manage your symptoms and help you feel better. To do this, SEROQUEL must be taken every day as instructed by your doctor, even after your symptoms have improved or disappeared.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING SEROQUEL?

Before starting SEROQUEL, 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 SEROQUEL (see "WHAT IS IN SEROQUEL AND WHAT DO THE TABLETS LOOK LIKE?" below)
- 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 SEROQUEL,
- If you are breast-feeding or are planning on breast-feeding while taking SEROQUEL. You should not breast-feed while taking SEROQUEL.
- If you drink alcohol or use street drugs.
- If you have diabetes or a family history of diabetes.
- If you have a history of liver, heart or kidney problems.
- If you exercise vigorously or work in hot or sunny places

SOME IMPORTANT THINGS I SHOULD KNOW ABOUT STARTING MY TREATMENT WITH SEROQUEL

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

Feelings of drowsiness are also common at the start of treatment, or when your dose is increased. Therefore, 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 SEROQUEL does not cause you to be drowsy.

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 SEROQUEL, your doctor may advise you that a specific type of eye exam is recommended in order to maximize safe use of this drug.

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

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 SEROQUEL.

HOW SHOULD I BE TAKING SEROQUEL?

In order for SEROQUEL 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 your symptoms to improve slowly over the first few weeks of treatment. Do not stop taking SEROQUEL, or change the times of day you take SEROQUEL, without talking to your doctor first.

To make sure you are getting the most benefit from SEROQUEL, you must:

- continue taking SEROQUEL 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 SEROQUEL for you.

You may take SEROQUEL with or without food.

Do not give SEROQUEL to anyone else. Your doctor has prescribed SEROQUEL for you only.

WHAT ARE POSSIBLE SIDE EFFECTS WITH SEROQUEL?

Like any medication, SEROQUEL may produce side effects in some people.

Dizziness, drowsiness and light-headedness are the most common side affects experienced by people taking SEROQUEL. The dizziness and drowsiness are usually mild and should go away with time (see also "SOME IMPORTANT THINGS I SHOULD KNOW ABOUT STARTING MY TREATMENT WITH SEROQUEL").

Other possible side effects include:

- headache
- constipation
- dry mouth
- upset stomach or abdominal pain
- some weight gain
- changes in laboratory tests for liver and thyroid functions.

Although rare with SEROQUEL use, this type of medication can cause muscle twitching or abnormal movements of your face and tongue. If you experience any of these effects, tell your doctor immediately.

One of the most important things for you to do to minimize the risks from side effects, while helping SEROQUEL 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.

WHAT SHOULD I DO IN CASE OF SEROQUEL OVERDOSE?

In case of SEROQUEL overdose or if you think you, or anyone else, are experiencing severe episodes of any of the above side effects of SEROQUEL (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.

CAN I TAKE OTHER MEDICATIONS WITH SEROQUEL?

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 SEROQUEL. As well, be sure to tell them about any other medications - prescription, non-prescription or alternative - that you are taking or plan to take.

WHAT DO I DO IF I MISS A DOSE OF SEROQUEL?

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 SEROQUEL:

- Take your SEROQUEL at the same time every day;
- Take SEROQUEL 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 SEROQUEL 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 SEROQUEL;
- Keep a written reminder to take your SEROQUEL 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.

WHERE SHOULD I KEEP SEROQUEL?

Store SEROQUEL at room temperature (between 15 - 30°C) and well out of the reach of children. The expiry date of this medicine is printed on the package label. Do not use the medicine after this date. If your doctor tells you to stop taking SEROQUEL or you find that they have passed their expiry date, please return any left over medicine to your pharmacist.

WHAT IS IN SEROQUEL AND WHAT DO THE TABLETS LOOK LIKE?

SEROQUEL tablets contain the active ingredient quetiapine fumarate. Other inactive ingredients in SEROQUEL tablets include: povidone, calcium hydrogen phosphate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydryoxypropyl methylcellulose, polyethylene glycol, titanium dioxide, yellow ferric oxide (25 mg, 100 mg and 150 mg tablets only) and red ferric oxide (25 mg tablets only).

SEROQUEL comes in five tablet strengths: 25 mg (round, peach colour), 100 mg (round, yellow colour), 150 mg (round, pale yellow colour), 200 mg (round, white colour) and 300 mg (capsule-shaped, white colour). The word "SEROQUEL" and the strength are written on each tablet. These words are easy to read on the tablets and if you see them you know you are taking the right medicine.

Important Note: This leaflet alerts you to some of the times you should call your doctor while you are taking SEROQUEL. Other situations that cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using SEROQUEL.

NOTE: This “INFORMATION FOR THE CONSUMER” Leaflet provides you with the most current information at the time of printing. Please refer to the Consumer Information Leaflet located at www.astrazeneca.ca, under the heading “Patients with Prescriptions”, to see if more up-to-date information has been posted.

Customer Inquiries: 1 800 668-6000

AstraZeneca Canada Inc.
Mississauga, Ontario
L4Y 1M4. 01/2006

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).

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.

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 SEROQUEL should have minimal EPS liability.

Pharmacology of Metabolites

Quetiapine and several of its metabolites 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 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/m2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid

gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

Cataracts

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/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, nor 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.

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

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

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 (S. 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_fSD 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_fSD 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_fSD 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.

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

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

BIBLIOGRAPHY

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.

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.

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

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.

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.

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

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.

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.

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

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.

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

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

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.

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.