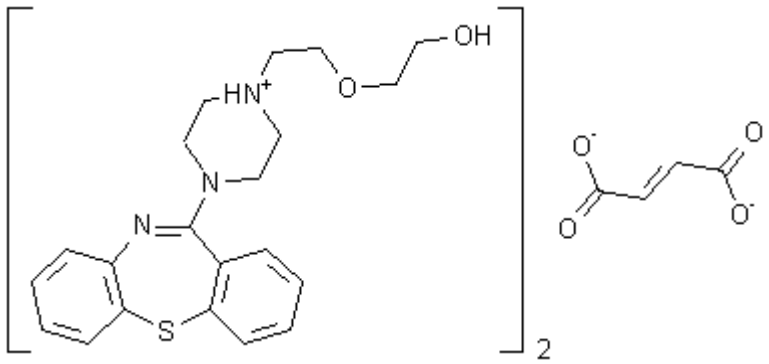
PRODUCT INFORMATION
QUETIAPINE SANDOZ® 25/100/200/300 mg FILM-COATED TABLETS

NAME OF THE MEDICINE
Quetiapine fumarate

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

Quetiapine fumarate has no chiral centres and only one morphological entity has been detected throughout development.

Structural Formula:



CAS Number: 111974-72-2

Empirical formula: $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ MW: 883.11

DESCRIPTION
Quetiapine fumarate is a weak acid (pKa 3.3, 6.8) which exhibits moderate pH dependent solubility (94.3mg/mL to 2.37mg/mL at pH values from 1 to 9) and lypophilicity characteristics (Log P) which vary with pH (0.45 in water, 1.37 at pH 5, 2.65 at pH 7 and 2.59 at pH 9).

Quetiapine fumarate displays good solid state stability, has an aqueous solubility of 3.29mg/mL at 25°C and exhibits suitable tableting properties when combined with appropriate excipients.

Quetiapine Sandoz 25mg, 100mg, and 200mg are round, film-coated tablets. Quetiapine Sandoz 300mg is capsoid, film-coated tablets.

Quetiapine Sandoz 25mg, 100mg, 200mg and 300mg tablets contain quetiapine fumarate equivalent to 25mg, 100mg, 200mg and 300mg quetiapine free base respectively. The inactive ingredients are: povidone, calcium hydrogen phosphate dihydrate, microcrystalline cellulose, lactose monohydrate, sodium starch glycollate A,

colloidal silica, magnesium stearate, hypromellose, macrogol 4000, titanium dioxide, iron oxide yellow C177492 (25mg and 100mg) and iron oxide red C177491 (25mg).

PHARMACOLOGY

Pharmacodynamics

Quetiapine is an atypical antipsychotic agent. Quetiapine and the human plasma metabolite, norquetiapine, interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors; this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2 receptors is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effects (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to quetiapine's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic $alpha_1$ receptors and moderate affinity at adrenergic $alpha_2$ receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes, which may explain anti-cholinergic (muscarinic) effects. The norquetiapine metabolite 7-hydroxy norquetiapine also has affinity for histaminergic H_1 and $5HT_{2B}$ and $5HT_{2C}$ receptors at clinically relevant concentrations.

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also reverses the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2 receptor blockade. The extent to which the metabolites norquetiapine and 7-hydroxy norquetiapine contribute to the pharmacological activity of quetiapine in humans is uncertain.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2 receptor super sensitivity 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 depolarisation blockade of the mesolimbic but not the 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.

It has been demonstrated that quetiapine is effective when given once or 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 are maintained for up to 12 hours. The safety and efficacy of doses greater than 800mg/day have not been evaluated.

Pharmacokinetics

Absorption

Quetiapine is well absorbed and the bioavailability of quetiapine is not significantly affected by administration with food.

Distribution
The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours respectively. Quetiapine is approximately 83% bound to plasma proteins. Steady state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosage range. The kinetics of quetiapine do not differ between men and women.

Metabolism
Quetiapine is extensively metabolised by the liver following oral administration, with parent compound accounting for less than 5% of unchanged drug related material in the urine or faeces, following the administration of radiolabelled quetiapine. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

In vitro investigations established that CYP3A4 is likely to be the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4. CYP2D6 and CYP2C9 are also involved in quetiapine metabolism.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak to modest inhibitors of human cytochrome P450 3A4, 2C19, 2D6, 1A2 and 2C9 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 800mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other medicines will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

Following oral administration of a single-dose of quetiapine 25mg to healthy subjects under fasting conditions, a mean peak plasma concentration (C_{max}) of quetiapine of approximately 66.50ng/mL was achieved within approximately 1 hour (T_{max}).

Following oral administration of a single-dose of quetiapine 100mg to healthy subjects under fasting conditions, a mean peak plasma concentration (C_{max}) of quetiapine of approximately 421.42ng/mL was achieved within approximately 1 hour (T_{max}).

Excretion
Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces.

Use in renal impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30

mL/min/1.73m^2), but the individual clearance values are within the range for normal subjects.

Use in hepatic impairment
The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects. 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 (see DOSAGE AND ADMINISTRATION).

Pre-clinical data
Acute toxicity studies
Quetiapine has low acute toxicity. Findings in mice (median lethal dose >500mg/kg PO; 100mg/kg IP), rats (median lethal dose >500mg/kg PO; 100mg/kg IP) and dogs (dose limit study 10-75mg/kg PO) were typical of neuroleptic agents and included decreased motor activity, ptosis, loss of righting reflex, prostration, fluid around the mouth and convulsions.

Repeat-dose toxicity studies
In multiple-dose studies in rats, dogs and monkeys, 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, and 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 was seen in mice, rats and monkeys. This hypertrophy was secondary to compensatory elevations of circulating Thyroid Stimulating Hormone (TSH) brought about by increased hepatic metabolism of thyroid hormones.

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

Transient increases in heart rate were not accompanied by consistent effects on blood pressure in dogs.

Posterior triangular cataracts seen after 6 months in dogs at 100mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225mg/kg/day, although an increase in lens relucency was seen at the highest dose. No effects on the lens were seen in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man (see

ADVERSE EFFECTS – Clinical study experience – Other findings observed during clinical studies).

No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies, however there was evidence for reduced lymphocytes in the bone marrow of dogs and in the circulation of monkeys.

CLINICAL TRIALS

Bipolar disorder (adults)

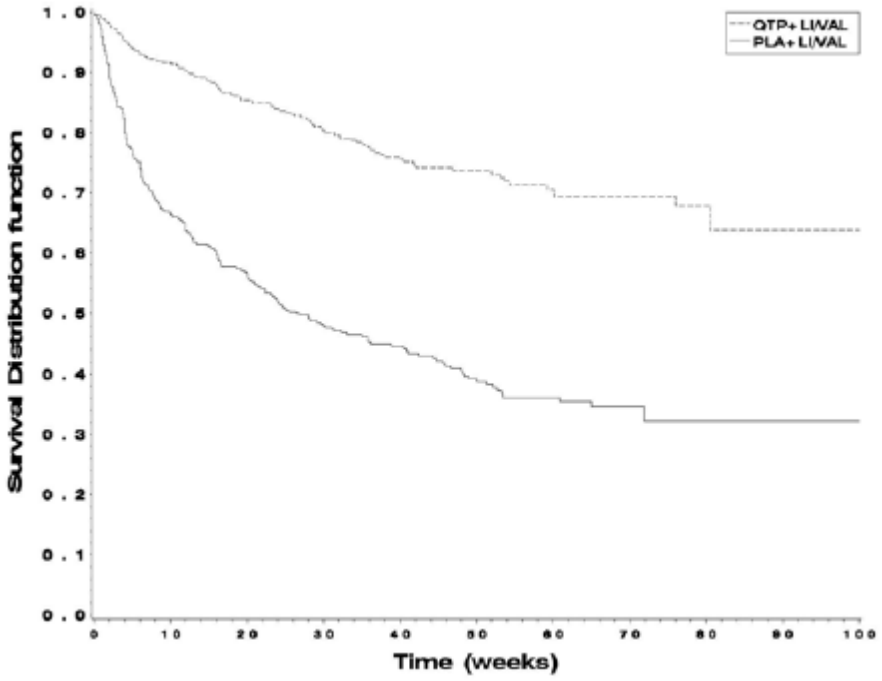
Maintenance treatment in combination with lithium or sodium valproate

The efficacy of quetiapine in the maintenance treatment of bipolar disorder was established in two similarly designed placebo-controlled trials in patients who met DSM-IV criteria for bipolar I disorder. These trials included patients whose most recent mood episode was mania (approximately 36%), depression (approximately 30%) or mixed state (approximately 34%); and patients with or without psychotic features. Patients with rapid cycling (approximately 37%) were also included.

Both trials consisted of an open label phase followed by a randomised treatment phase. In the open label phase (n=3414), patients were required to be stabilised on quetiapine (400 – 800mg/day) in combination with a mood stabiliser (lithium or valproate) for at least 12 weeks prior to randomisation. In the randomisation phase, patients who were symptomatically stable for at least 12 weeks (n=1326) either continued treatment with quetiapine (at the same dose, then adjusted as clinically indicated) in combination with a mood stabiliser or received placebo in combination with a mood stabiliser for up to 104 weeks. Approximately 40% of patients received lithium and 60% received valproate.

The primary endpoint was time to recurrence of any mood event (mania, depression or mixed state). A mood event was defined as medication initiation, hospitalisation, Young Mania Rating Scale (YMRS) score ≥20 or Montgomery-Asberg Depression Rating Scale (MADRS) score ≥20 on two consecutive assessments or study discontinuation due to a mood event. Quetiapine was superior to placebo in increasing the time to recurrence of a mood event in both studies. Patients on quetiapine had a 70% less risk of experiencing a recurrence of a mood event (refer Figure 1 and Table 1) compared to patients on placebo. Patients on quetiapine had a lower risk of experiencing a mood event prior to week 28 and week 52 compared to patients on placebo (refer Table 2).

Figure 1. Time to recurrence of a mood event for the combined maintenance treatment studies, Kaplan Meier curves (ITT population)



ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate.

Table 1 Summary of efficacy results (ITT population) for maintenance treatment

	Study 1	**Study 2**	**Combined studies**
	QTP + LI/VAL vs PLA + LI/VAL QTP N=336 / PLA N=367	**QTP + LI/VAL vs PLA + LI/VAL QTP N=310 / PLA N=313**	**QTP + LI/VAL vs PLA + LI/VAL QTP N=646 / PLA N=680**
Analysis of time to recurrence of a mood event			
Hazard ratio [95% CI]	0.28 [0.21, 0.37]	0.32 [0.24, 0.42]	0.30 [0.24, 0.37]
p-value	<0.0001	<0.0001	<0.0001
Analysis of time to recurrence of a manic event			
Hazard ratio [95% CI]	0.30 [0.20, 0.44]	0.30 [0.18, 0.49]	0.30 [0.22, 0.41]
p-value	<0.0001	<0.0001	<0.0001
Analysis of time to recurrence of a depression event			
Hazard ratio [95% CI]	0.26 [0.17, 0.41]	0.33 [0.23, 0.48]	0.30 [0.23, 0.40]
p-value	<0.0001	<0.0001	<0.0001
ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.			

Table 2 Kaplan Meier estimates of mood, manic and depressive event rates at weeks 28 and 52 (ITT population) – combined studies

Kaplan Meier survival estimate of event rates (%)			
Time to event	**QTP + LI/VAL (N=646)**	**PLA + LI/VAL (N=680)**	**p value**
Mood event rates			
Week 28	82.5%	49.7%	<0.0001
Week 52	73.7%	38.8%	<0.0001
Manic event rates			
Week 28	91.9%	73.6%	<0.0001
Week 52	86.0%	63.8%	<0.0001
Depressive event rates			
Week 28	89.9%	68.4%	<0.0001
Week 52	85.8%	61.8%	<0.0001
ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.			

Maintenance treatment with quetiapine was superior to placebo in increasing the time to recurrence of a depressive or a manic event (refer Table 1). Patients on quetiapine also had a lower risk of experiencing a depressive or a manic event prior to week 28 and week 52 compared to patients on placebo (refer to Table 2).

Efficacy was demonstrated to be independent of the nature of the most recent episode (manic, mixed or depressed), the mood stabiliser (lithium or valproate), rapid cycling course, gender, age or ethnicity.

Acute Mania

The efficacy of quetiapine in the treatment of manic episodes was established in three short-term placebo-controlled 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 or mixed episodes.

The primary outcome variable for these trials was change from baseline to Day 21 in the YMRS total score, an instrument used to assess manic symptoms. Various secondary outcomes were also assessed. The Clinical Global Impression-Bipolar (CGI-BP) Version reflects the clinician's impression of the severity of the patient's overall bipolar illness and improvement from baseline (CGI-BP Severity and CGI-BP Improvement). In addition, MADRS was used to assess depressive symptoms, and the Positive and Negative Symptoms Scale (PANSS) was used to assess the efficacy in psychosis, agitation and aggression. The Global Assessment Scale (GAS) was used to assess improvement in functional status.

The results of the trials follow:

In two 12-week trials (n=300, n=299) comparing quetiapine to placebo, quetiapine was superior to placebo in reducing manic symptoms. Of those patients with a clinical response, 87% received doses of quetiapine between 400 and 800mg per day. The mean last week median dose of quetiapine in responders was approximately 600mg/day.

The majority of patients who responded at day 21 maintained responses to day 84. On secondary endpoints, quetiapine was also clinically and statistically superior to placebo.

Improvements were observed in CGI-BP Severity and Improvement, MADRS total score, PANSS total score, PANSS activation subscale and in the GAS score. The effectiveness of quetiapine was unaffected by age, gender, ethnicity or the presence of psychotic symptoms at baseline.

In a 3-week placebo controlled trial (n=170) comparing quetiapine to placebo in patients on a mood stabiliser (lithium or valproate), quetiapine was superior to placebo in reducing manic symptoms. Improvements were observed in CGI-BP Severity and Improvement and PANSS total score. Of those patients with a clinical response, 91% received doses of quetiapine between 400 and 800mg per day. The mean last week median dose of quetiapine in responders was approximately 600mg/day. In a similarly designed 6-week placebo controlled trial (n=200) quetiapine demonstrated a similar improvement in YMRS scores but did not demonstrate superiority to placebo at either day 21 or day 42, possibly due to a higher placebo effect.

Schizophrenia (adults)
The efficacy of quetiapine was established in short-term controlled trials of psychotic inpatients who met DSM III-R criteria for schizophrenia. Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), CGI and Scale for Assessing Negative Symptoms (SANS).

The main trials were:

1. A 6-week placebo-controlled trial (n=361) involving 5 fixed doses of quetiapine (75, 150, 300, 600 and 750mg/day on a three times a day dosing schedule).

2. A 6-week placebo-controlled trial (n=109) involving titration of quetiapine in doses up to 750mg/day on a three times a day dosing schedule.

3. A 6-week placebo-controlled (n=286) involving titration of quetiapine in high (up to 750mg/day on a three times a day dosing schedule) and low (up to 250mg/day on a three times a day dosing schedule) doses.

4. A 6-week dose and dose regimen comparison trial (n=618) involving 2 fixed doses of quetiapine (450mg/day on both twice a day and three times a day dosing schedules and 50mg/day on a twice a day dosing schedule).

Quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In a comparative clinical trial of 10 weeks duration, quetiapine has been shown to be as effective as risperidone, using a 40% or more decline in the baseline PANSS score as a definition of response; although statistically comparative efficacy was not demonstrated when using a 30% decline in PANSS score, the differences between treatments were modest in absolute terms and in all probability not clinically meaningful.

INDICATIONS
Quetiapine Sandoz is indicated for:

Bipolar disorder
Adults
- Maintenance treatment of bipolar I disorder, in combination with lithium or sodium valproate, for the prevention of recurrence of manic, depressive or mixed episodes
- Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate

Schizophrenia
Adults
- Treatment of schizophrenia

CONTRAINDICATIONS
Quetiapine Sandoz is contraindicated in patients who are hypersensitive to any component of this product.

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

Quetiapine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from pre-marketing clinical studies. Because of the risk of orthostatic hypotension with quetiapine, caution should be observed in cardiac patients.

Orthostatic hypotension
Quetiapine may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope especially during the initial dose titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope has been commonly reported (see ADVERSE EFFECTS). Orthostatic hypotension, dizziness and syncope may lead to falls (see ADVERSE EFFECTS). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate

QT interval
In clinical trials, quetiapine was not associated with a persistent increase in QT_c intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (see OVERDOSAGE), in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT

interval. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Particularly in the elderly, the use of quetiapine should be avoided in combination with neuroleptics and medicines that are known to prolong QT_c including Class Ia antiarrhythmics (e.g. disopyramide) or Class III antiarrhythmics (e.g. amiodarone, sotalol), antipsychotic medications (e.g. ziprasidone, chlorpromazine, haloperidol), antibiotics (e.g. moxifloxacin, erythromycin), or any other class of medications known to prolong the QT_c interval (e.g. citalopram, pentamidine, methadone). Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsades de pointes and/or sudden death, including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalemia or hypomagnesmia; (3) concomitant use of other medicines that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval.

Cardiomyopathy and myocarditis
Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Seizures
In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo (see ADVERSE EFFECTS). As with other antipsychotics, caution is recommended when treating patients with a history of seizures or with conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Clinical worsening and suicide risk associated with psychiatric disorders
The risk of suicide attempt is inherent in depression and may persist until significant remission occurs. The risk must be considered in all depressed patients.

Patients with depression may experience worsening of their depressive symptoms and/or the emergence of suicidal ideation and behaviour (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored for clinical worsening and suicidality, especially at the beginning of a course of treatment or at the time of dose changes, either increases or decreases. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset or was not part of the patient's presenting symptoms.

Patients (and caregivers of patients) should be alerted about the need to monitor for any worsening of their condition and/or the emergence of suicidal ideation/behaviour or thoughts of harming themselves and to seek medical advice immediately if these symptoms present. Patients with comorbid depression associated with other psychiatric disorders being treated with antidepressants should be similarly observed for clinical worsening and suicidality.

Pooled analysis of 24 short-term (4 to 16 weeks) placebo controlled trials of nine antidepressant medicines (SSRIs and others) in 4,400 children and adolescents with major depressant disorder (16 trials), obsessive compulsive disorder (4 trials) or other psychiatric disorders (4 trials) have revealed a greater risk of adverse events representing suicidal behaviour or thinking (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients treated with an antidepressant was 4% compared with 2% of patients taking a placebo. There was considerable variation in risk among the antidepressants but there was a tendency towards an increase for almost all antidepressants studied. This meta-analysis did not include trials involving quetiapine.

The risk of suicidality was most consistently observed in the major depressive disorder trials but there were signals of risk arising from the trials in other psychiatric indications (obsessive compulsive disorder and social anxiety disorder) as well. No suicides occurred in these trials. It is unknown whether the suicidality risk in children and adolescent patients extends to use beyond several months. The nine antidepressant medicines in the pooled analyses included five SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) and four non-SSRIs (bupropion, mirtazapine, nefazodone, venlafaxine).

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either worsening of depression and/or emergence of suicidal impulses has not been established there is concern that such symptoms may be precursors of emerging suicidality.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or for any other condition (psychiatric or nonpsychiatric) should be informed about the need to monitor these patients for the emergence of agitation, irritability, unusual changes in behaviour and other symptoms described above, as well as emergence of suicidality, and to report such symptoms immediately to health care providers. It is particularly important that monitoring be undertaken during the initial few months of antidepressant treatment or at times of dose increase or decrease.

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

Prescriptions for quetiapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

In clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adults less than 25 years of age who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively).

In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Weight
Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines (see ADVERSE EFFECTS).

Venous thromboembolism (VTE)
Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Extrapyramidal symptoms (EPS)
In placebo controlled clinical trials of adult patients with schizophrenia, bipolar mania and maintenance treatment of bipolar disorder, the incidence of EPS was no different from that of placebo across the recommended therapeutic dose range. In short-term, placebo-controlled clinical trials for bipolar depression, the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients (see ADVERSE EFFECTS) for rates of EPS observed in all indications.

Class effect: Akathisia has been reported in patients treated with quetiapine. The presentation of akathisia may be variable and comprises subjective complaints of restlessness and an overwhelming urge to move and either distress or motor phenomena such as pacing, swinging of the legs while seated, rocking from foot to foot, or both. Particular attention should be paid to the monitoring for such symptoms and signs as, left untreated, akathisia is associated with poor compliance and an increased risk of relapse.

Tardive dyskinesia
Quetiapine should be prescribed in a manner that is most likely to minimise the occurrence of tardive dyskinesia.

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

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see ADVERSE EFFECTS).

Neuroleptic malignant syndrome
Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase.

In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing quetiapine for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Neutropenia and agranulocytosis
Severe neutropenia ($<0.5 \times 10^9$/L) without infection has been uncommonly reported in clinical trials with quetiapine. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine during clinical trials (rare) as well as post-marketing reports (including fatal cases). Most of these cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC), a history of drug induced neutropenia and concomitant use of other medicines that have been associated with neutropenia.

There have been cases of agranulocytosis in patients without pre-existing risk factors. Neutropenia should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate.

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 EFFECTS).

Hepatic enzyme inducers
Concomitant use of quetiapine with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of quetiapine may need to be considered if quetiapine is used concomitantly with a hepatic enzyme inducer.

CYP3A4 inhibitors
During concomitant administration of medicines which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of quetiapine should be used. 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 (see INTERACTIONS WITH OTHER MEDICINES).

Hyperglycaemia and diabetes mellitus
Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including quetiapine (see ADVERSE EFFECTS). 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.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. **Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment.** Any patient treated with atypical antipsychotics should be monitored for symptoms of 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.

Lipids
Increases in triglycerides, LDL and total cholesterol, and decreases in fasting HDL cholesterol have been observed in clinical trials with quetiapine (see ADVERSE EFFECTS). Monitoring is recommended at baseline and periodically during treatment for all patients. Lipid changes should be managed as clinically appropriate.

Metabolic factors
In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies. All patients taking antipsychotic medications such as quetiapine should be monitored for metabolic factors at the start of treatment and at intervals during treatment in accordance with current local guidelines. The results of monitoring should be managed as clinically appropriate.

Pancreatitis
Pancreatitis has been reported in clinical trials and during post marketing experience. Among the post marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see Lipids section, above, and in Effects on laboratory tests), gallstones and alcohol consumption.

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

For patients who have known or suspected abnormal hepatic function prior to starting quetiapine, standard clinical assessment, including measurement of transaminase levels is recommended. Periodic clinical reassessment with transaminase levels is recommended for such patients, as well as for patients who develop any signs and symptoms suggestive of a new onset liver disorder during quetiapine therapy (see ADVERSE EFFECTS).

Increased risk of mortality in elderly patients with dementia-related psychosis
Elderly patients with dementia-related psychosis treated with atypical anti-psychotics are at an increased risk of death compared to placebo. A meta-analysis of seventeen placebo controlled trials with dementia related behavioural disorders showed a risk of death in the drug-treated patients of approximately 1.6 to 1.7 times that seen in placebo-treated patients. The clinical trials included in the meta-analysis were undertaken with olanzapine, aripiprazole, risperidone, and quetiapine. Over the course of these trials averaging about 10 weeks in duration, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g. pneumonia) in nature. Quetiapine is not approved for the treatment of elderly patients with dementia-related psychosis or behavioural disorders.

Withdrawal
Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of antipsychotic medicines including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see ADVERSE EFFECTS).

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

Dysphagia
Oesophageal dysmotility and aspiration have been associated with antipsychotic drug use. Quetiapine and other antipsychotic medicines should be used cautiously in patients at risk for aspiration pneumonia (e.g. elderly patients).

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see ADVERSE EFFECTS). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation.

Lactose monohydrate
Quetiapine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Effects on fertility
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.

Use in pregnancy - Category C
Australian Pregnancy Category C: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects.

The safety and efficacy of quetiapine during human pregnancy have not been established.

Non-teratogenic class effect: Neonates exposed to antipsychotic medicines (including quetiapine) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring. Quetiapine should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Teratogenic effects were not observed following administration of quetiapine at oral doses up to 200mg/kg in rats (less than the exposure to quetiapine at the maximum recommended clinical dose based on AUC) and 100mg/kg in rabbits (approximately twice the maximum clinical exposure based on BSA).

Use in lactation
There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. In a study in lactating rats the concentration of quetiapine and/or its metabolites was higher in milk than in plasma. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine.

Paediatric use (10 to 17 years of age)
The safety and efficacy of Quetiapine Sandoz has not been established in patients under 18 years of age.

Genotoxicity
Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen. Quetiapine showed no evidence of genotoxicity in a series of assays for gene mutation

(bacteria and Chinese hamster ovary cells) and chromosomal damage (human lymphocytes and the *in vivo* micronucleus test).

Carcinogenicity
In the rat study (20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia. The incidence of carcinoma of the adrenal cortex was increased in male rats at the highest dose.

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.

Effects on laboratory tests
Leukopenia and/or neutropenia
As with other antipsychotics transient leukopenia and/or neutropenia have been observed in patients administered quetiapine. There were no cases of persistent severe neutropenia reported in controlled clinical trials with quetiapine. During post-marketing experience, resolution of leukopenia and/or neutropenia has followed cessation of therapy with quetiapine. Possible risk factors for leukopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leukopenia and/or neutropenia. Occasionally, eosinophilia has been observed (see ADVERSE EFFECTS).

Serum transaminase
Asymptomatic elevations in serum transaminase (ALT, AST) or γ-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment (see ADVERSE EFFECTS).

Lipids
Increases in triglyceride levels and total cholesterol (predominantly LDL cholesterol) have been observed during treatment with quetiapine. Decreases in fasting HDL cholesterol have also been observed (see ADVERSE EFFECTS).

Thyroid hormone levels
Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T_4 - 3.4% for quetiapine versus 0.6% for placebo; free T_4 - 0.7% for quetiapine versus 0.1% for placebo; total T_3 - 0.54% for quetiapine versus 0.0% for placebo and free T_3 - 0.2% for quetiapine versus 0.0% for placebo. The incidence of shifts in TSH was 3.2 % for quetiapine versus 2.7% for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T_4 and TSH. As supported by the literature, these changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first 6 weeks of quetiapine treatment, with no further reduction during long-term treatment.

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 ADVERSE EFFECTS).

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

Effect on ability to drive and use machines
Somnolence has been very commonly reported in patients treated with quetiapine. Given its primary central nervous system effects, quetiapine has the potential to impair judgement, thinking or motor skills. Patients likely to drive or operate other machines should therefore be cautioned appropriately.

Sleep apnoea
In patients who have a history of or are at risk for sleep apnoea, and are receiving concomitant central nervous system (CNS) depressants, quetiapine should be used with caution.

Anti-cholinergic (muscarinic) effects
Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to adverse drug reactions reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see PHARMACOLOGY, INTERACTIONS WITH OTHER MEDICINES, ADVERSE EFFECTS and OVERDOSAGE).

INTERACTIONS WITH OTHER MEDICINES

Antipsychotic and other centrally acting medicines
Given the primary central nervous system effects, quetiapine should be used with caution in combination with other centrally acting medicines and alcohol.

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

Lorazepam
The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20 % in the presence of quetiapine administered as 250 mg three times a day dosing. Dosage adjustment is not required.

Levodopa and dopamine agonists
As it exhibits *in vitro* dopamine antagonism, quetiapine may antagonise the effects of levodopa and dopamine agonists.

Carbamazepine and phenytoin
See Hepatic enzyme inducers, below.

Potential interactions that have been excluded
Antipsychotics
The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone (3mg twice a day) or haloperidol (7.5mg twice a day). The pharmacokinetics of lithium was not altered when co-administered with quetiapine (250mg three times a day). The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.

Imipramine and fluoxetine
See CYP inhibitors, below.

CYP inhibitors
CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine (see Metabolism section). CYP2D6 and CYP2C9 are also involved.

CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics and protease inhibitors)
During concomitant administration of medicines which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials (see *Ketoconazole,* below). As a consequence of this lower doses of quetiapine should be used. Special consideration should be given in elderly or debilitated patients. The risk-benefit ratio needs to be considered on an individual basis.

It is also not recommended to take quetiapine together with grapefruit juice.

Ketoconazole
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 (200mg once daily for 4 days) resulted in an increase in mean C_{max} and AUC of quetiapine of 335% 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.

Potential interactions that have been excluded
Cimetidine
The pharmacokinetics of quetiapine (150mg three times a day) were not significantly altered (20% decrease in clearance) following co-administration with cimetidine (400mg three times a day for 4 days) a known P450 enzyme inhibitor. Dosage adjustment for quetiapine is not required when it is given with cimetidine.

Imipramine and fluoxetine
The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (75 mg twice a day; a known CYP2D6 inhibitor) or fluoxetine (60 mg once daily; a known CYP3A4 and CYP2D6 inhibitor).

Hepatic enzyme inducers (e.g. carbamazepine and phenytoin)
Quetiapine (administration of multiple daily doses up to 750 mg/day, on a three times a day dosing schedule) did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, concomitant use of quetiapine with hepatic enzyme inducers such as carbamazepine or phenytoin may substantially decrease systemic exposure to quetiapine (see Carbamazepine and phenytoin below). Depending on clinical response, increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and hepatic enzyme inducers (e.g. carbamazepine, phenytoin, barbiturates, rifampicin, glucocorticoids). The safety of doses above 800 mg/day has not been established in the clinical trials. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient.

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

Carbamazepine and phenytoin
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.

Co-administration of quetiapine (250 mg three times a day) and phenytoin (100 mg three times a day; another microsomal enzyme inducer) also caused increases in clearance of quetiapine by 5-fold.

Cardiovascular medicines
Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

Caution should be used when quetiapine is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT_c interval.

Because of its potential for inducing hypotension, quetiapine may enhance the effects of certain anti-hypertensive medicines.

Medications to manage attention deficit hyperactivity disorder (ADHD)
The data regarding safety and efficacy of quetiapine for the treatment of bipolar mania in children and adolescents receiving psychostimulants for co-morbid ADHD are limited. Therefore, concomitant use of ADHD medication and quetiapine is not recommended. If concomitant therapy is considered necessary, patients should be carefully monitored for the effect of the combination of treatments on the signs and symptoms of both ADHD and acute mania. Effects on blood pressure may be cumulative and blood pressure should be carefully monitored.

Anti-cholinergic (muscarinic) effects
Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see PRECAUTIONS).

ADVERSE EFFECTS

Clinical Study Experience

Schizophrenia (adults)
The treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks) of schizophrenia in at least 1% [rounded to the nearest percent] of patients treated with quetiapine in placebo-controlled Phase-II/III trials where the incidence in patients treated with quetiapine was greater than the incidence in placebo-treated patients are listed in Table 3 regardless of causality.

Table 3 Adverse events that occurred in at least 1% of patients treated with quetiapine for schizophrenia in placebo-controlled Phase-II/III trials[1]

Body system/Adverse event[2]	Number (%) of patients with adverse events	
	Quetiapine [n=510]	Placebo [n=206]
Body as a whole		
Headache	19%	18%
Asthenia	4%	3%
Abdominal pain	3%	1%
Back pain	2%	1%
Fever	2%	1%
Nervous system		
Somnolence	18%	11%
Dizziness	10%	4%
Digestive system		
Constipation	9%	5%
Dry mouth	7%	3%
Dyspepsia	6%	2%
γ-GT increased	2%	1%
Cardiovascular system		
Postural hypotension	7%	2%
Tachycardia	7%	5%
Metabolic and nutritional disorders		
ALT increased	6%	2%
AST increased	4%	1%
Weight gain	2%	0%
Skin and appendages		
Rash	4%	3%
Respiratory system		

Body system/Adverse event[2]	Number (%) of patients with adverse events	
	Quetiapine [n=510]	Placebo [n=206]
Rhinitis	3%	1%
Haemic and lymphatic system		
Leukopenia	2%	0%
Special senses		
Ear pain	1%	0%

n=number of patients in treatment group
[1] Events for which the quetiapine incidence was equal to or less than placebo are not listed in the table, but included the following: pain, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhoea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paraesthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.
[2] Adverse events recorded where the incidence in patients treated with quetiapine was greater than the incidence in placebo-treated patients.

Bipolar I Disorder – Acute Mania (adults)

Adverse events that occurred during the treatment of acute mania in 5% or more of patients treated with quetiapine in either the monotherapy or adjunct therapy, placebo controlled trials and observed at a rate of at least twice that of placebo are listed in Table 4 regardless of causality.

Table 4 Adverse events observed in at least 5% of patients treated with quetiapine as monotherapy or in combination with a mood stabiliser (lithium or valproate) for acute mania in bipolar I disorder

	Quetiapine mono-therapy		Quetiapine adjunct therapy					
			Randomised treatment		Assigned mood stabilizer			
	Number (%) of patients with adverse events							
Event	**QTP N=209**	**PLA N=198**	**QTP+ LI/VAL N=196**	**PLA+ LI/VAL N=203**	**QTP+ LI N=122**	**PLA+ LI N=128**	**QTP+ VAL N=74**	**PLA+ VAL N=75**
Somnolence	16.3%	4.0%	33.7%	9.4%	30.3%	5.5%	39.2%	16.0%
Dry mouth	15.8%	3.0%	19.4%	3.0%	17.2%	3.1%	23.0%	2.7%
Weight gain	9.1%	1.5%	6.1%	2.5%	4.9%	2.3%	8.1%	2.7%
Dizziness	6.7%	2.5%	9.2%	6.4%	4.9%	3.9%	16.2%	10.7%
Asthenia	5.3%	2.0%	9.7%	3.9%	4.9%	3.1%	17.6%	5.3%
Pharyngitis	2.4%	2.0%	5.6%	2.5%	4.1%	2.3%	8.1%	2.7%
Postural hypotension	4.3%	1.5%	6.6%	1.5%	3.3%	0.8%	12.2%	2.7%

PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.

Bipolar I Disorder – Maintenance (adults)

The safety results of two clinical trials show that quetiapine tablets are generally safe and well tolerated when used in combination with lithium or valproate in long-term treatment. Adverse events occurring at an incidence of 5% or more in any randomised treatment group from placebo-controlled clinical trials in patients with bipolar I disorder treated with quetiapine in combination with lithium or valproate as maintenance therapy is summarised by randomised treatment and by assigned mood stabiliser for the combined studies in Table 5 regardless of causality.

Table 5 Adverse events observed in at least 5% of patients (randomised safety population) treated with quetiapine in adjunctive maintenance trials for bipolar I disorder

	Number (%) of patients with adverse events					
	Randomized treatment		Assigned mood stabilizer			
MedDRA preferred term[a]	**QTP+LI/VAL (N=646)**	**PLA +LI/VAL (N=680)**	**QTP+LI (N=274)**	**PLA+LI (N=287)**	**QTP+VAL (N=372)**	**PLA+VAL (N=393)**
Headache	7.4%	9.3%	9.1%	10.5%	6.2%	8.4%
Nasopharyngitis	7.1%	7.2%	6.6%	7.3%	7.5%	7.1%
Upper respiratory tract infection	6.7%	4.0%	7.7%	4.9%	5.9%	3.3%
Insomnia	6.5%	16.6%	8.0%	19.5%	5.4%	14.5%
Tremor	6.0%	5.0%	5.1%	6.3%	6.7%	4.1%
Nausea	5.9%	7.6%	8.8%	11.8%	3.8%	4.6%
Diarrhoea	2.9%	6.0%	3.3%	8.0%	2.7%	4.6%

[a] Patients with multiple events falling under the same preferred term are counted only once in that term. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group. MedDRA Medical Dictionary of Regulatory Activities.

Adverse events occurring at an incidence of 5% or more in any randomised treatment group from placebo-controlled clinical trials in patients with bipolar I disorder treated with quetiapine as monotherapy maintenance therapy is summarised by randomised treatment in Table 6 regardless of causality.

Table 6 Adverse events observed in at least 5% of patients (randomised safety population) treated with quetiapine in monotherapy maintenance trials for bipolar I disorder

	Number (%) of patients with adverse events		
MedDRA preferred term[a]	**Quetiapine (N=404)**	**Placebo (N=404)**	**Lithium (N=418)**
Headache	36 (8.9)	32 (7.9)	48 (11.5)
Somnolence	27 (6.7)	17 (4.2)	11 (2.6)
Insomnia	26 (6.4)	69 (17.1)	52 (12.4)
Nausea	18 (4.5)	33 (8.2)	53 (12.7)
Tremor	12 (3.0)	8 (2.0)	31 (7.4)
Diarrhoea	11 (2.7)	21 (5.2)	26 (6.2)
Vomiting	8 (2.0)	12 (3.0)	47 (11.2)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term. N Number of patients in treatment group. MedDRA Medical Dictionary of Regulatory Activities.

Bipolar Depression (adults)

The safety results of four placebo controlled clinical trials show quetiapine tablets are generally safe and well tolerated when used for treatment of bipolar depression. All four studies contained an 8 week acute phase with 2 of these studies containing a continuation phase of an additional 52 weeks. Adverse events occurring at an incidence of 5% or more in any treatment group in the acute phase for the combined studies are summarised in Table 7 regardless of causality.

Adverse events occurring at an incidence of 5% or more in any treatment group in the continuation phase for the combined studies are summarised in Table 8 regardless of causality.

Table 7 Adverse events observed in at least 5% of patients (safety population) in any treatment group in the acute phase of bipolar depression trials

	Number (%) of patients with adverse events		
MedDRA preferred term[a]	**Quetiapine 300mg N=853**	**Quetiapine 600mg N=859**	**Placebo N=602**
Dry mouth	28.4%	29.8%	8.8%
Somnolence	22.6%	21.4%	6.3%
Sedation	18.2%	18.3%	6.0%
Dizziness	12.5%	15.4%	6.3%
Headache	9.4%	9.2%	16.3%
Constipation	7.2%	9.3%	3.0%
Fatigue	6.4%	8.1%	5.5%
Nausea	6.0%	8.3%	10.3%
[a] Patients with multiple events falling under the same preferred term are counted only once in that term. N Number of patients in treatment group. MedDRA Medical Dictionary of Regulatory Activities.			

Table 8 Adverse events (treatment emergent only[b]) observed in at least 5% of patients (safety population) in any treatment group in the continuation phase of bipolar depression trials

	Number (%) of patients with adverse events		
MedDRA preferred term[a]	**Quetiapine 300mg N=141**	**Quetiapine 600mg N=150**	**Placebo N=294**
Headache	13.5%	11.3%	9.5%
Nasopharyngitis	9.9%	2.7%	5.4%
Nausea	7.1%	2.0%	3.7%
Diarrhoea	5.7%	0.7%	1.7%
Dry mouth	3.5%	6.0%	1.4%
[a] Patients with multiple events falling under the same preferred term are counted only once in that term. [b] Events first reported or worsened intensity during continuation phase. N Number of patients in treatment group. MedDRA Medical Dictionary of Regulatory Activities.			

Other findings observed during clinical studies

Somnolence

Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine. Somnolence may lead to falls.

Weight Gain (adults)

In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight from baseline were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for quetiapine (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo.

Withdrawal (discontinuation symptoms)

In acute placebo-controlled monotherapy clinical trials in adults which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was 16.0% for quetiapine and 7.3% for placebo. The aggregated

incidence of individual adverse events (e.g. insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) did not exceed 6.7% in any treatment group and usually resolved after 1 week post-discontinuation (see PRECAUTIONS).

Leukopenia/Neutropenia
Possible risk factors for leukopenia and/or neutropenia include pre-existing low white cell count and history of drug induced leukopenia and/or neutropenia. Neutrophil count decreases have commonly been observed. In all short-term placebo controlled monotherapy clinical trials in adults, 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 1.9% in patients treated with quetiapine, compared to 1.5% in placebo-treated patients. The incidence ≥ 0.5 - $< 1.0 \times 10^9$/L (moderate neutropenia) was 0.2% (uncommon) in patients treated with quetiapine and 0.2% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count $< 1.0 \times 10^9$/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 (severe neutropenia) was 0.21% (uncommon) in patients treated with quetiapine and 0% in placebo treated patients (see PRECAUTIONS).

Lipid changes (adults)
In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol $\geq$6.2064 mmol/L and triglycerides $\geq$2.258 mmol/L were 16% and 23% for quetiapine treated patients respectively compared to 7% and 16% for placebo treated patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for quetiapine treated patients respectively, compared to 6% and 9% for placebo treated patients respectively.

In placebo controlled trials decreases in fasting HDL cholesterol have been observed. In short-term placebo-controlled clinical trials the incidence of patients who shifted from $\geq$1.025 mmol/L to <1.025 mmol/L was slightly higher in the quetiapine group compared to placebo (9.8% and 8.1% respectively). In long-term trials the incidence of patients who shifted from $\geq$1.025 mmol/L to <1.025 mmol/L was 18.3% in quetiapine and 10.9% in placebo.

Increases in blood glucose levels
In placebo-controlled clinical trials in adults, the percentage of patients who had a shift to a high blood glucose level (fasting blood glucose $\geq$7 mmol/L or a non-fasting blood glucose $\geq$11.1 mmol/L on at least one occasion) was 5.1% in patients treated with quetiapine and 4.2% in placebo treated patients (see PRECAUTIONS).

Decreases in haemoglobin levels
Decreased haemoglobin to 8.07 mmol/L males, 7.45 mmol/L females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. In short-term placebo controlled trials, decreased haemoglobin to 8.07 mmol/L males, 7.45 mmol/L females on at least one occasion in 8.3% of quetiapine patients compared to 6.2% of placebo patients.

Extrapyramidal Symptoms (adults)
The following clinical trials in adult patients included treatment with quetiapine immediate release and modified release tablets. In short-term placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregate incidence of EPS was similar to placebo (schizophrenia: quetiapine 7.8%, placebo 8.0%; bipolar mania quetiapine 11.2%, placebo 11.4%). In two long-term clinical trials in bipolar maintenance the incidence of EPS from randomisation to end of treatment was 7.9% for quetiapine (in combination with a mood stabiliser) compared to 6.9% for placebo (in combination with a mood stabiliser). In short-term placebo-controlled trials in clinical trials in bipolar depression the aggregate incidence of EPS from the combined data was 8.9% for quetiapine compared to 3.8% for placebo though the incidence of the individual adverse events (e.g. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. In long-term studies of schizophrenia and bipolar disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo (see PRECAUTIONS - Extrapyramidal symptoms and Table 9 below).

Irritability
In acute placebo-controlled clinical trials in patients ≥18 years of age, the incidence of irritability was 2.3% for quetiapine and 1.7% for placebo.

Dysphagia
An increase in the rate of dysphagia with quetiapine vs placebo was only observed in the adult clinical trials in bipolar depression.

Other adverse drug reactions
In addition to the above the following adverse medicine reactions have also been observed in adult clinical trials (placebo-controlled trials, active-arm controlled trials and open-label uncontrolled trials) with quetiapine.

Table 9

Frequency	**System Organ Class**	**Event**
Very common (≥10%)	Nervous system disorders	Extrapyramidal symptoms
	General disorders and administration site conditions	Withdrawal (discontinuation) symptoms
	Blood and lymphatic system disorders	Decreased haemoglobin
	Metabolism and nutritional disorders	Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol
	Gastrointestinal disorders	Dry mouth
Common (≥1% to <10%)	Endocrine disorders	Hyperprolactinemia

Frequency	**System Organ Class**	**Event**
	Eye disorders	Vision blurred
	General disorders and administration site conditions	Peripheral oedema, irritability, pyrexia, mild asthenia
	Investigations	Elevations in serum alanine transaminases (ALT)[8] and aspartame aminotransferase (AST)[8], elevations in ɤ-GT levels[8], elevations in serum prolactin[3], decreases in total T_4, free T_4 and total T_3 and increases in TSH[5], decreased neutrophil count; eosinophils increased[7]
	Metabolism & nutritional disorders	Increased appetite, increased blood glucose to hyperglycaemic levels
	Nervous system disorders	Syncope[2], dysarthria, extrapyramidal symptoms
	Psychiatric disorders	Abnormal dreams and nightmares
	Cardiac disorders	Tachycardia, palpitations[4]
	Gastrointestinal disorders	Vomiting[6], dyspepsia, constipation
	Respiratory, thoracic and mediastinal disorders	Dyspnoea[4], rhinitis
	Blood disorder	Leukopenia
	Vascular disorders	Orthostatic hypotension
Uncommon (≥0.1% to <1%)	Blood and lymphatic system disorders	Eosinophilia, thrombocytopenia, anaemia, decreased platelet count
	Gastrointestinal disorders	Dysphagia[2]
	Investigations	Decreased platelet count[1], decreases in free T_3 [5]
	Immune system disorders	Hypersensitivity
	Nervous system disorders	Syncope [2], seizure[2], restless legs syndrome, tardive dyskinesia[2]
	Metabolism & nutritional disorders	Hyponatraemia, diabetes mellitus

Frequency	**System Organ Class**	**Event**
	Reproductive system and breast disorders	Sexual dysfunction
	Respiratory, thoracic and mediastinal disorders	Rhinitis
	Renal and urinary disorders	Urinary retention
	Cardiac disorders	Bradycardia[9], QT prolongation
	Endocrine disorders	Decrease in free $T_{3,}$ hypothyroidism
Rare (≥0.01% to <0.1%)	General disorders and administration site conditions	Neuroleptic malignant syndrome[2], hypothermia
	Investigations	Elevations in blood creatine phosphokinase (not associated with neuroleptic malignant syndrome), agranulocytosis[10]
	Reproductive system and breast disorders	Priapism, galactorrhoea, breast swelling, menstrual disorder
	Vascular disorders	Venous thromboembolism
	Psychiatric disorders	Somnambulism and other related events
	Gastrointestinal disorders	Intestinal obstruction/Ileus; Pancreatitis
	Blood and lymphatic system disorders	Agranulocytosis[10]
	Metabolism and nutritional disorders	Metabolic syndrome
	Hepato-biliary disorders	Hepatitis (with or without jaundice)
Very Rare <0.01%)	Immune system disorders	Anaphylactic reaction
	Endocrine disorders	Inappropriate antidiuretic hormone secretion
	Musculoskeletal and connective tissue disorders	Rhabdomyolysis
Not known	General disorders and administration site conditions	Neonatal withdrawal[11]

[1]. Platelets ≤100 x 10^9 /L on at least one occasion
[2]. See PRECAUTIONS
[3.] Prolactin levels (patients ≥18 years of age): >200µg/L males; >30µg/L females at any time.
[4.]These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease

Frequency	System Organ Class	Event
[5.] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.08x LLN (pmol/L) and shift in TSH is >5mIU/L at any time. [6.] Based upon the increased rate of vomiting in elderly patients (≥ 65 years of age). [7.] Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as≥1 x 10^9 cells/L at any time [8] Asymptomatic elevations (shift from normal to ≥3 x ULN at any time) in serum transaminases (ALT and AST) or γ-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment. [9]May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine. [10] Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia (<0.5 x 10^9/L) and infection. [11] See USE IN PREGNANCY		

Children and adolescents (schizophrenia and acute mania)

The incidence of common (≥5%) adverse events that occurred in children and adolescent (10-17 years) in two short-term treatment placebo-controlled trials in schizophrenia and biopolar mania is listed below in Table 10 regardless of causality.

Table 10 Adverse events that occurred in at least 5% of child/adolescent patients treated with quetiapine tablets in short term schizophrenia and bipolar mania studies (pooled safety analysis set)

	Number (%) of patients with adverse events	
Preferred term	Quetiapine* (N=340)	Placebo (N=165)
Somnolence	29.4%	8.5%
Sedation	16.2%	4.2%
Dizziness	15.3%	3.6%
Headache	14.7%	17.0%
Fatigue	8.8%	4.2%
Increased Appetite	7.6%	2.4%
Dry mouth	7.1%	0.6%
Insomnia	6.8%	14.5%
Nausea	6.8%	10.3%
Tachycardia	6.8%	0%
Vomiting	6.5%	5.5%
Agitation	5.6%	9.7%
Weight increased	5.0%	1.2%
* 400-800 mg/day; N – number of patients		

The adverse events ≥5% reported in a 26-week, open-label clinical trial with quetiapine product in children and adolescents with schizophrenia and bipolar mania were: somnolence (22.9%), headache (18.7%), sedation (14.2%), weight increased (13.4%), vomiting (10.8%), nausea (9.5%), dizziness (8.7%), fatigue (8.2%), insomnia (8.2%), increased appetite (7.1%), upper respiratory tract infection (6.8%), agitation (5.3%), irritability (5.0%), tachycardia (5.0%).

Comparison to adult adverse drug reactions
The same adverse drug reactions described above for adults should be considered for children and adolescents. The following table summarises adverse drug reactions that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or adverse drug reactions that have not been identified in the adult population.

Frequency	**System Organ Class**	**Event**
Very common (≥10%)	Metabolism and nutritional disorders	Increased appetite
	Investigations	Elevations in serum prolactin[1], increases in blood pressure[2]
	Nervous system disorders	Extrapyramidal symptoms
	Gastrointestinal disorders	Vomiting
Common (≥1% to <10%)	Respiratory, thoracic & mediastinal disorders	Rhinitis
	Nervous system disorders	Syncope

[1] Prolactin levels (patients <18 years of age): >20 µg/L males; >26 µg/L females at any time. Less than 1% of patients had an increase to a prolactin level >100 µg/L
[2] Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents

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

In these trials of patients with schizophrenia the incidence of suicidal related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥25 years of age, and 1.4% (2/147) for quetiapine and 1.3% (1/75) for placebo in patients <18 years of age.

In these trials of patients with bipolar mania the incidence of suicide related events was 0% for quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both quetiapine (6/496) and placebo (6/503) in patients ≥25 years of age, and 1.0% (2/193) for quetiapine and 0% (0/90) for placebo in patients <18 years of age.

In these trials of patients with bipolar depression the incidence of suicide related events was 3.0% (7/233) for quetiapine and 0% (0/120) for placebo in patients 18-24 and 1.8% for both quetiapine and 0% (19/1616) and placebo (11/622) in patients ≥25 years of age. There have been no trials conducted in patients <18 years of age with bipolar depression (see PRECAUTIONS).

Cataracts/lens opacities
In a clinical trial to evaluate the cataractogenic potential of quetiapine tablets (200 - 800 mg/day) versus risperidone (2 - 8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in quetiapine compared with risperidone for patients with at least 21 months of exposure (see Preclinical data).

Post-marketing experience
In addition to the above, the following post-marketing adverse drug reactions have been observed with quetiapine.

Table 11

Frequency	System Organ Class	Reaction
Rare (≥0.01 - <1%)	Reproductive system & breast disorders	galactorrhea
Very rare (<0.01%)	Immune system disorders	anaphylactic reaction

Very rare cases of cataract and urinary retention have been reported in the post-marketing data, but no causal link between these reports and quetiapine has been established.

There have been rare post-marketing reports of pancreatitis. Among the post-marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see discussion on Lipids and Effects on laboratory tests in the PRECAUTIONS section, above), gallstones and alcohol consumption.

Very rare cases of exacerbation of pre-existing diabetes have been reported.

Very rare post-marketing cases of tardive dyskinesia and very rare post-marketing cases of other EPS related events (e.g. dyskinesia, tremor, muscle spasm, dystonia, muscle twitching) have been received (see PRECAUTIONS).

Very rare post-marketing cases of anaphylactic reaction have been received.

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

Other adverse events reported since market introduction, which were temporarily related to quetiapine therapy, but not necessarily causally related, include: cardiomyopathy, myocarditis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia, cerebrovascular accident Stevens-Johnson Syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS).

DOSAGE AND ADMINISTRATION
Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic medicines,

and (2) for whom alternative equally effective but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory response should be sought. The need for continued treatment should be reassessed periodically.

Quetiapine Sandoz should be administered twice daily, with or without food.

Bipolar disorder
Maintenance treatment
Adults
Patients who have responded to Quetiapine Sandoz for acute treatment of bipolar disorder should continue therapy at the same dose. It is generally recommended that responding patients be continued beyond the acute response, but at the lowest possible dose needed to maintain remission.

Quetiapine Sandoz in combination with a mood stabiliser, demonstrated efficacy at a total daily dose of 400mg to 800mg (refer CLINICAL TRIALS section).

The dose of Quetiapine Sandoz can be re-adjusted depending on the clinical response and tolerability of the individual patient. Patients should be periodically reassessed to determine the need for maintenance treatment.

Acute mania
Adults
The total daily dose for the first four days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4), alone or in combination with a mood stabiliser. Further dosage adjustments up to 800 mg/day by day 6 should be in increments of no greater than 200 mg/day.

The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 200 to 800 mg/day. The usual effective dose is in the range of 400 to 800 mg/day.

Schizophrenia
Adults
The total daily dose for the first four days of therapy is 50mg (Day 1), 100mg (Day 2), 200mg (Day 3) and 300mg (Day 4).

From Day 4 onwards, the dose should be titrated to the usual effective dose of 300 to 450mg/day. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750mg/day.

Elderly
As with other antipsychotics, Quetiapine Sandoz should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly subjects when compared with younger patients.

Children and adolescents
The safety and efficacy of Quetiapine Sandoz have not been evaluated in children and adolescents.

Renal impairment
Dosage adjustment is not necessary.

Hepatic impairment
Quetiapine is extensively metabolised by the liver. Therefore, Quetiapine Sandoz should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 25mg/day. The dose should be increased in increments of 25 to 50mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

OVERDOSAGE
Contact the Poisons Information Centre on 13 11 26 for advice on management.

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams and with patients recovering without sequelae. However, death has been reported in a clinical trial following an overdose of 13.6g of quetiapine alone.

In post marketing experience, there have been very rare reports of overdose of Quetiapine Sandoz alone resulting in death or coma or QT-prolongation.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see PRECAUTIONS – Concomitant cardiovascular illness).

In general, reported signs and symptoms were those resulting from an exaggeration of the medicines known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects.

Management of Overdose
There is no specific antidote to quetiapine. In cases of severe signs, 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. Whilst the prevention of absorption in overdose has not been investigated, administration of activated charcoal together with a laxative should be considered.

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

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

PRESENTATION AND STORAGE CONDITIONS

QUETIAPINE SANDOZ 25mg is presented as a peach coloured, round, film-coated tablet; available in blister packs and bottles of 60 tablets
QUETIAPINE SANDOZ 100mg is presented as a yellow coloured, round, scored on one side, film-coated tablet; available in blister packs and bottles of 90 tablets
QUETIAPINE SANDOZ 200mg is presented as a white coloured, round, scored on one side, film-coated tablet; available in blister packs and bottles of 60 tablets
QUETIAPINE SANDOZ 300mg is presented as a white coloured, capsoid in shape, scored on both sides, film-coated tablet; available in blister packs and bottles of 60 tablets

Not all presentations may be marketed in Australia.

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 726 369

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

28/04/2011

DATE OF MOST RECENT AMENDMENT

26/09/2017