

AUSTRALIAN PRODUCT INFORMATION

QUETIAPINE APOTEX (QUETIAPINE FUMARATE) TABLETS

1 NAME OF THE MEDICINE

Quetiapine fumarate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Quetiapine APOTEX tablets contain quetiapine fumarate equivalent to 25 mg, 100 mg, 200 mg and 300 mg quetiapine free base respectively.

Excipients with known effect

Lactose monohydrate

For the full list of excipients see section **6.1 List of Excipients**

3 PHARMACEUTICAL FORM

Quetiapine APOTEX (25 mg tablets) are presented as a pink coloured, round, biconvex, film-coated tablets plain on both side; each tablet contains 25 mg of quetiapine (as fumarate).

Quetiapine APOTEX (100 mg tablets) are presented as a yellow coloured, round, biconvex, film-coated tablet plain on both sides; each tablet contains 100 mg of quetiapine (as fumarate).

Quetiapine APOTEX (200 mg tablets) are presented as a white to off white, round, biconvex, film-coated tablet, plain on both sides; each tablet contains 200 mg of quetiapine (as fumarate).

Quetiapine APOTEX (300 mg tablets) are presented as a white to off white, capsule shaped, biconvex, film-coated tablet, with '300' debossed on one side and plain on other side; each tablet contains 300 mg of quetiapine (as fumarate).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Quetiapine APOTEX tablets are indicated for:

Bipolar disorder

Adults

- Maintenance treatment of bipolar I disorder, as monotherapy or in combination with lithium or sodium valproate, for the prevention of relapse/recurrence of manic, depressive or mixed episodes
- Treatment of depressive episodes associated with bipolar disorder (see section **4.2 Dose and method of administration**)
- Treatment of acute mania associated with bipolar I disorder as monotherapy or in combination with lithium or sodium valproate

Children/adolescents aged 10 to 17 years

- Monotherapy treatment of acute mania associated with bipolar I disorder

Schizophrenia (adults and adolescents aged 13 to 17 years)

- Treatment of schizophrenia

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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 drugs, 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 tablets can be administered with or without food.

Adults

Bipolar disorder

Maintenance treatment

Quetiapine tablets should be administered twice daily.

Patients who have responded to quetiapine 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.

For prevention of relapse/recurrence of manic, depressive and mixed episodes in bipolar disorder, the usual effective dose is within the range of 300 to 800 mg/day (See section **5.1 Pharmacodynamic properties - Clinical Trials**).

The dose of quetiapine 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.

Bipolar depression

When treating depressive episodes in bipolar disorder, treatment should be initiated either by the treating psychiatrist or by the general practitioner after consultation with the psychiatrist.

Quetiapine tablets should be administered once daily at bedtime.

Quetiapine should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The dose may be adjusted up to 600 mg/day in increments of 100 mg/day depending on the clinical response and tolerability of the individual patient.

Acute mania

Quetiapine should be administered twice daily. 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

Quetiapine should be administered twice daily. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4).

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

Elderly

As with other antipsychotics, quetiapine 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 immediate release tablets have been evaluated in children and adolescents 10 to 17 years of age with bipolar mania (as monotherapy), and 13 to 17 years of age with schizophrenia.

Quetiapine tablets should be administered twice daily. However, quetiapine tablets may be administered three times daily based on response and tolerability.

Acute mania - monotherapy (10 to 17 years of age)

The total daily dose for the first five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After Day 5, the dose should be adjusted within the effective dose range of 400 to 600 mg/day depending upon the clinical response and tolerability of the patient. Patients should be administered the lowest effective dose. Dosage adjustments should be in increments of no greater than 100 mg/day.

Schizophrenia (13 to 17 years of age)

The total daily dose for the first five days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3), 300 mg (Day 4) and 400 mg (Day 5). After Day 5, the dose should be adjusted within the effective dose range of 400 to 800 mg/day depending upon the clinical response and tolerability of the patient. Patients should be administered the lowest effective dose. Dosage adjustments should be in increments of no greater than 100 mg/day.

Renal impairment

Dosage adjustment is not necessary.

Hepatic impairment

Quetiapine is extensively metabolised by the liver. Therefore, quetiapine 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 25 mg/day. The dose should be increased in increments of 25 to 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 CONTRAINDICATIONS

Quetiapine APOTEX tablets are contraindicated in patients who are hypersensitive to any component of this product.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 section **4.8 Adverse effects (Undesirable effects)**). Orthostatic hypotension, dizziness and syncope may lead to falls (see section **4.8 Adverse effects (Undesirable 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 QTc intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose (see section **4.9 Overdose**). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients, including children and adolescents, with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed with medicines known to prolong the QTc interval, and concomitant neuroleptics, especially the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life threatening adverse drug reactions that have been reported during quetiapine exposure. SCARs commonly present as a combination of the following symptoms: extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia. Discontinue quetiapine if severe cutaneous adverse reactions occur.

Seizures

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo (see section **4.8 Adverse effects (Undesirable 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 depressive 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, mirtazepine, 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.

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. 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 preventative 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 section **4.8 Adverse effects (Undesirable 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 dyskinesia 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 section **4.8 Adverse effects (Undesirable 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, eg, 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 short term placebo controlled monotherapy 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 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 $1.5 \times 10^9/L$). See section **4.8 Adverse effects (Undesirable 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 drugs 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 section **4.5 Interactions with other medicines and other forms of interactions**).

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 section **4.8 Adverse effects (Undesirable 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 and cholesterol, and decreases in fasting HDL cholesterol have been observed in clinical trials with quetiapine (see section **4.8 Adverse effects (Undesirable 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 section **4.8 Adverse effects (Undesirable 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 nausea, vomiting and insomnia 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 section **4.8 Adverse effects (Undesirable 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

Esophageal 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 (eg elderly patients).

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section **4.8 Adverse effects (Undesirable 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

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

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 **sections 5.1 Mechanism of Action, Section 4.5 Anticholinergic (muscarinic) effects, Section 4.8 Adverse effects (Undesirable effects) and Section 4.9 Overdose**).

Use in the elderly

See sections **4.2 Dose and method of administration - Use in the elderly, 4.8 Adverse effects (Undesirable effects), 5.1 Pharmacodynamic properties - Clinical Trials and 5.2 Pharmacokinetic properties - Special patient populations/Use in the elderly**.

Paediatric use

(10 to 17 years of age)

Paediatric schizophrenia and bipolar I disorder are serious mental disorders, however, diagnosis can be challenging. For paediatric schizophrenia, symptom profiles can be variable, and for bipolar I disorder, patients may have variable patterns of periodicity of manic or mixed symptoms. It is recommended that medication therapy for paediatric schizophrenia and bipolar I disorder be initiated only after a thorough diagnostic evaluation has been performed and careful consideration given to the potential benefits and risks associated with medication treatment. Medication treatment for both paediatric schizophrenia and bipolar I disorder is indicated as part of a total treatment program that often includes psychological, educational and social interventions.

Efficacy and safety of quetiapine have been demonstrated for adolescents aged from 13 years with schizophrenia and for children/adolescents aged from 10 years with bipolar I disorder experiencing acute mania in two clinical trials of 6 and 3 weeks duration, respectively. Safety data was provided for up to 26 weeks in a third open-label safety and tolerability trial (see section **5.1 Pharmacodynamic properties - Clinical trials –Children and adolescents**). The safety and efficacy of quetiapine in children and adolescents have not been assessed beyond these time periods.

Although not all adverse reactions that have been identified in adult patients have been observed in clinical trials with quetiapine in children and adolescent patients, the same precautions that appear above for adults should be considered for children and adolescents. As seen in adults, increases in TSH, serum cholesterol, triglycerides, and weight have been observed (see sections **4.4 Special warnings and precautions for use – Effects on laboratory tests** and **4.8 Adverse effects (Undesirable effects)**).

The following events were reported more frequently in the short-term studies in children and adolescents than in studies in adults: EPS, increases in appetite and serum prolactin. Increased blood pressure has not been identified in the adult population but was seen in children and adolescents. Blood pressure should be monitored at the beginning of, and periodically during treatment in children and adolescents (see section **4.8 Adverse effects (Undesirable effects)**).

Long-term safety data including growth, maturation and behavioural development, beyond 26 weeks of treatment with quetiapine, are not available for children and adolescents (10 to 17 years of age).

Effects on laboratory tests

Leukopenia and/or neutropenia

As with other antipsychotics transient leukopenia and/or neutropenia have been observed in patients administered 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 section **4.8 Adverse effects (Undesirable 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 section **4.8 Adverse effects (Undesirable effects)**).

Lipids

Increase 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 section **4.8 Adverse effects (Undesirable effects)**).

Thyroid hormone levels

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total and free T₄ was maximal within the first 6 weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T₄, irrespective of the duration of treatment. see section **4.8 Adverse effects (Undesirable effects)**.

About 0.7% (26/3489) of quetiapine adult patients experienced TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the adult mania adjunct studies, 12% (24/196) of the quetiapine treated patients compared to 7% (15/203) placebo treated patients had elevated TSH levels.

In acute placebo-controlled studies in children and adolescent patients with schizophrenia or bipolar mania the incidence of shifts to potentially clinically important thyroid function values at any time for Quetiapine and placebo treated patients for elevated TSH was 2.9% vs 0.7% respectively, and for decreased total thyroxine was 2.8% vs 0% respectively. Of the Quetiapine treated patients with elevated TSH levels, 1 had a simultaneous low free T₄ level at the end of treatment.

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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Antipsychotic and other centrally acting medicines

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

Thioridazine

Thioridazine (200 mg twice a day) increased the oral clearance of quetiapine (300 mg 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 (3 mg twice a day) or haloperidol (7.5 mg twice a day). The pharmacokinetics of lithium were not altered when co-administered with quetiapine (250 mg 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 section **5.2 Pharmacokinetic properties - Metabolism**). CYP2D6 and CYP2C9 are also involved.

CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics and protease inhibitors)

During concomitant administration of drugs 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 (refer **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 (200 mg 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 (150 mg three times a day) were not significantly altered (20% decrease in clearance) following co-administration with cimetidine (400 mg 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

Caution should be used when quetiapine is used concomitantly with medicines known to cause electrolyte imbalance or to increase QTc 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 section 4.4 **Special warnings and precautions for use**).

4.6 FERTILITY, PREGNANCY AND LACTATION

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

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

Non-teratogenic class effect: Neonates exposed to antipsychotic drugs (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 200 mg/kg in rats (less than the exposure to quetiapine at the maximum recommended clinical dose based on AUC) and 100 mg/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.

4.7 EFFECTS 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 immediate release tablets 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 1 regardless of causality.

Table 1 Adverse events that occurred in at least 1% of patients treated with quetiapine for schizophrenia in placebo-controlled Phase-II/III trials¹

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		
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 SEROQUEL 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 immediate release tablets 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 2 regardless of causality.

Table 2 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

Event	Quetiapine monotherapy		Quetiapine adjunct therapy					
	QTP N=209	PLA N=198	Randomised treatment		Assigned mood stabilizer			
			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
Number (%) of patients with adverse events								
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 immediate 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 3 regardless of causality.

Table 3 Adverse events observed in at least 5% of patients (randomised safety population) treated with quetiapine in adjunctive maintenance trials for bipolar I disorder

Preferred term ^a	Number (%) of patients with adverse events					
	Randomized treatment		Assigned mood stabilizer			
	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.

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 94 regardless of causality.

Table 4 Adverse events observed in at least 5% of patients (randomised safety population) treated with quetiapine in monotherapy maintenance trials for bipolar I disorder

Preferred term ^a	Number [n (%)] of patients with adverse events		
	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. n Number of patients.

Bipolar Depression (adults)

The safety results of four placebo controlled clinical trials show that quetiapine immediate release 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 5 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 6 regardless of causality.

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

Preferred term ^a	Number (%) of patients with adverse events		
	Quetiapine 300 mg N = 853	Quetiapine 600 mg 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.

Table 6 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

Preferred term ^a	Number (%) of patients with adverse events		
	Quetiapine 300 mg N = 141	Quetiapine 600 mg 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.

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 $\geq 7\%$ 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 (eg, 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 section **4.4 Special warnings and precautions for use - Withdrawal**).

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 placebo controlled monotherapy clinical trials, among patients with a baseline neutrophil count $\geq 1.5 \times 10^9/L$, the incidence of at least one occurrence of neutrophil count $< 1.5 \times 10^9/L$ was 1.72% in patients treated with quetiapine, compared to 0.73% in placebo-treated patients. The incidence $\geq 0.5 - 1.0 \times 10^9/L$ (moderate neutropenia) was uncommon in patients treated with quetiapine. 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 section **4.4 Special warnings and precautions for use - Neutropenia and agranulocytosis**).

Lipid changes (adults)

In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥ 6.2064 mmol/L and triglycerides ≥ 2.258 mmol/L were 16% and 23% for quetiapine immediate release tablets 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 ≥ 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 ≥ 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 ≥ 7 mmol/L or a non-fasting blood glucose ≥ 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 section **4.4 Special warnings and precautions for use - Hyperglycaemia and diabetes mellitus**).

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 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 short-term, placebo-controlled 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 also section **4.4 Special warnings and precautions for use - Extrapyramidal symptoms** and Table 7 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 drug reactions have also been observed in adult clinical trials (placebo-controlled trials, active-arm controlled trials and open-label uncontrolled trials) with quetiapine.

Table 7

Frequency	System Organ Class	Reaction
Very common ($\geq 10\%$)	Nervous system disorders	Extrapyramidal symptoms
Common ($\geq 1\%$ to $< 10\%$)	Cardiac disorders	Palpitations ⁴
	Eye disorders	Vision blurred
	Gastrointestinal disorders	Vomiting ⁶
	General disorders and administration site conditions	Peripheral oedema; Irritability; Pyrexia
	Investigations	Elevations in serum alanine transferase (ALT) ⁸ ; Elevations in γ -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 ; Eosinophils increased ⁷
	Metabolism & nutritional disorders	Increased appetite
	Nervous system disorders	Syncope ² ; Dysarthria

	Psychiatric disorders	Abnormal dreams and nightmares
	Respiratory, thoracic and mediastinal disorders	Dyspnoea ⁴
	Blood disorder	Leukopenia
Uncommon (≥0.1% to <1%)	Cardiac disorders	Bradycardia ⁹
	Gastrointestinal disorders	Dysphagia ²
	Investigations	Elevations in serum aspartate aminotransferase (AST) ⁸ ; Platelet count decreased ¹ ; Decreases in free T ₃ ⁵
	Immune system disorders	Hypersensitivity
	Nervous system disorders	Seizure ² ; Restless legs syndrome; Tardive dyskinesia ²
	Respiratory, thoracic and mediastinal disorders	Rhinitis
	Renal and urinary disorders	Urinary retention
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
	Psychiatric disorders	Somnambulism and other relevant events
	Reproductive system and breast disorders	Priapism
	Gastrointestinal disorders	Intestinal obstruction/Ileus
	Hepatobiliary disorders	Hepatitis (with or without jaundice)
Not known	General disorders and administration site conditions	Neonatal withdrawal ¹¹

1. Platelets $\leq 100 \times 10^9/L$ on at least one occasion
2. See section **4.4 Special warnings and precautions for use**
3. Prolactin levels (patients ≥ 18 years of age): $>20\mu g/L$ males; $>30\mu g/L$ females at any time
4. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease
5. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T₄, free T₄, total T₃ and free T₃ are defined as $<0.08 \times LLN$ (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 $\geq 1 \times 10^9$ cells/L at any time.
8. Asymptomatic elevations (shift from normal to $\geq 3 \times ULN$ at any time) in serum transaminases (ALT) 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 ($< 0.5 \times 10^9/L$) and infection.
11. See section 4.6 **Fertility, pregnancy and lactation, Use in Pregnancy**.

Children and adolescents

The incidence of common ($\geq 5\%$) adverse events that occurred in children and adolescent (10-17 years) in two short-term treatment placebo-controlled trials in schizophrenia and bipolar mania is listed below in Table 8 regardless of causality.

Table 8 Adverse events that occurred in at least 5% of child/adolescent patients treated with quetiapine immediate release tablets in short-term schizophrenia and bipolar mania studies (pooled safety analysis set)

Preferred term	Number (%) of patients with adverse events	
	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 $\geq 5\%$ reported in a 26-week, open-label clinical trial with quetiapine immediate release tablets 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 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.

Table 9

Frequency	System Organ Class	Reaction
Very common (≥10%)	Metabolism & nutrition disorders	Increased appetite
	Investigations	Elevations in serum prolactin ¹ ; Increases in blood pressure ²
	Gastrointestinal disorders	Vomiting
Common (≥1% - <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

Weight Gain (children and adolescents)

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. 21% of quetiapine-treated patients and 7% of placebo-treated patients gained ≥7% of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body Weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. 12% of quetiapine-treated patients and 0% of placebo-treated patients gained ≥7% of their body Weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increases in body weight and BMI were 4.4 kg and 1.1 kg/m² respectively. 45% of the patients gained ≥7% of their body weight, (not adjusted for normal growth). 18.3% of the patients had a clinically significant change in BMI (adjusted for growth).

Extrapyramidal Symptoms (EPS) [children and adolescents]

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

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 (75/9238) and placebo (37/4745).

In these trials of patients with schizophrenia the incidence of suicide related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients ≥ 25 years of age, 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 both quetiapine (0/60) and placebo (0/58) in patients 18-24 years of age, 1.2% for both

quetiapine (6/496) and placebo (6/503) in patients \geq 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 (19/1616) and placebo (11/622) in patients \geq 25 years of age. There have been no trials conducted in patients $<$ 18 years of age with bipolar depression (see section **4.4 Special warnings and precautions for use**).

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of quetiapine immediate release 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 section **5.3 Preclinical safety data**.

Post-marketing experience

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

Table 10

Frequency	System Organ Class	Reaction
Rare (\geq 0.01 - $<$ 1%)	Reproductive system & breast disorders	galactorrhea
Very rare ($<$ 0.01%)	Immune system disorders	anaphylactic reaction
Unknown	Skin and subcutaneous disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS)

Very rare cases of cataract 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 section **4.4 Special warnings and precautions for use**, above), gallstones and alcohol consumption.

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

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 section **4.4 Special warnings and precautions for use**).

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at <http://www.tga.gov.au/reporting-problems> and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

In clinical trials, experience with quetiapine in overdosage is limited. Estimated doses of quetiapine up to 30 g have been taken, without fatal consequences, and with patients recovering without sequelae, however, death has been reported in a clinical trial following an overdose of 13.6 g of quetiapine alone. In postmarketing experience, there have been very rare reports of overdose of quetiapine alone resulting in death or coma.

In post marketing experience there were cases reported of QT prolongation with overdose.

Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see section **4.4 Special warnings and precautions for use - Concomitant cardiovascular illness**).

In general, reported signs and symptoms were those resulting from an exaggeration of the drug's 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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 (5HT₂) and dopamine D₁ and D₂ receptors; this combination of receptor antagonism with a higher selectivity for 5HT₂ relative to D₂ receptors is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effects (EPS) liability of quetiapine compared to typical antipsychotics. Additionally, norquetiapine has high affinity (higher than quetiapine) for the noradrenaline transporter, 5HT_{1B} and muscarinic receptors. Quetiapine and norquetiapine also have high affinity at histaminergic H₁ and adrenergic α_{1B} and $_{1A}$ receptors, with a lower affinity at adrenergic α_2 and 5HT_{1A} receptors. Quetiapine has no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors. The norquetiapine metabolite 7-hydroxy norquetiapine also has affinity for histaminergic H₁ and 5HT_{2B} and _{2C} receptors at clinically relevant concentrations.

Pharmacodynamics

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 D₂ 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 D₂ receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D₂ receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing 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-naïve 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, 5HT₂ and D₂ receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

Clinical trials

Bipolar disorder (adults)

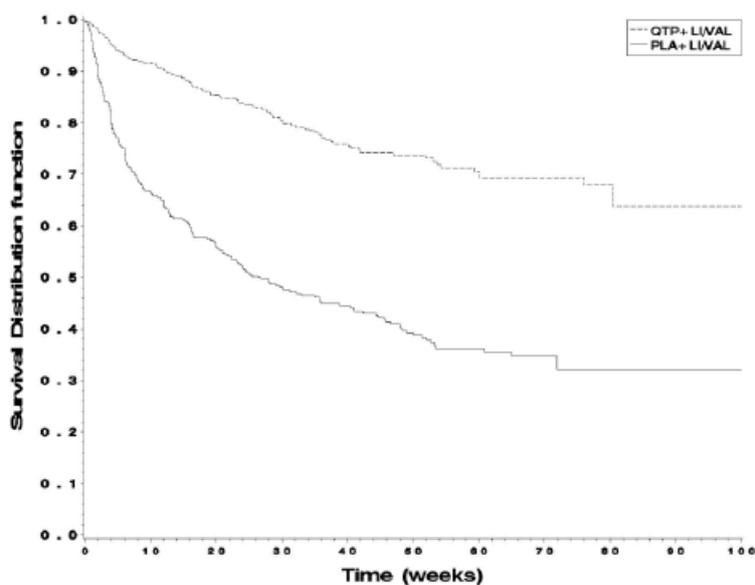
Maintenance treatment in combination with lithium or sodium valproate

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 – 800 mg/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 11) 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 12).

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 11 Summary of efficacy results (ITT population) for maintenance treatment

	Study 1 QTP + LI/VAL vs PLA + LI/VAL QTP N=336 / PLA N=367	Study 2 QTP + LI/VAL vs PLA + LI/VAL QTP N=310 / PLA N=313	Combined studies 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 first recurrence as 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 first recurrence as 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 12 Kaplan Meier estimates of mood, manic and depressive event rates at weeks 28 and 52 (ITT population) – combined studies

Time to event	Kaplan Meier survival estimate of event rates (%)		p value
	QTP + LI/VAL (N=646)	PLA + LI/VAL (N=680)	
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 tablets was superior to placebo in increasing the time to recurrence of a depressive or a manic event (refer Table 11). 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 12).

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

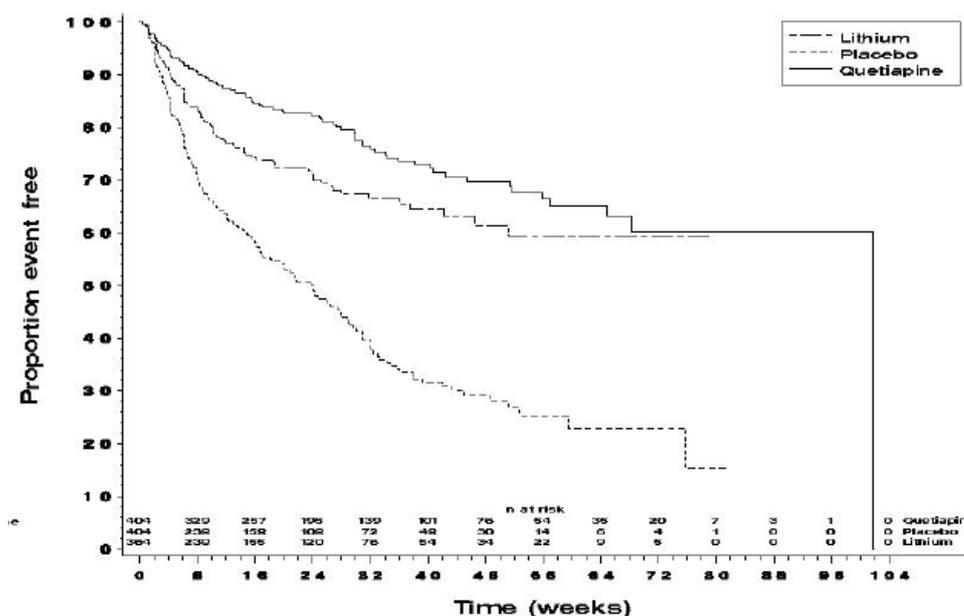
Maintenance treatment as monotherapy

The efficacy of quetiapine in the maintenance treatment of bipolar disorder as monotherapy was established in a placebo-controlled trial in 1172 patients who met DSM-IV criteria for bipolar I disorder. Approximately 50% of the 2438 patients initially treated with quetiapine for their index episode achieved stabilisation and were eligible for enrolment in the placebo-controlled randomised phase. The most recent mood episode of patients included was mania (approximately 54%), depression (approximately 28%) or mixed state (approximately 18%). Patients with rapid cycling were also included.

The trial consisted of an open label phase followed by a randomised treatment phase. In the open label phase, patients were required to be stabilised on quetiapine immediate release tablets (300 – 800 mg/day) for at least 4 weeks prior to randomisation to quetiapine, placebo or lithium. In the randomisation phase, the dose of quetiapine and lithium could be adjusted as clinically indicated. Randomised treatment was intended for up to 104 weeks however the study was stopped early following a positive interim analysis.

The primary endpoint was time to relapse/recurrence of any mood event (mania, depression or mixed state). A mood event was defined as medication initiation, hospitalisation, YMRS scores ≥ 20 or 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 relapse/recurrence of a mood event. Patients on quetiapine had a 71% less risk of experiencing a relapse/recurrence of a mood event (refer Figure 2 and Table 3) compared to patients on placebo. Quetiapine was also superior to placebo in increasing time to relapse/recurrence of manic events and depressed events (refer Table 3). Efficacy was demonstrated to be independent of the nature of the most recent episode (manic, mixed or depressive), rapid cycling course, gender, age or ethnicity.

Figure 2 Time to relapse/recurrence of a mood event, manic event and depressed event, Kaplan Meier curves (ITT population)



ITT Intent-to-treat. The numbers above the x-axis indicate the number of patients at risk of having an event at given time-points

Table 13 Summary of efficacy results (ITT population) for maintenance treatment

	Quetiapine vs Placebo N _{QTP} =404/ N _{PLA} =404	Lithium vs Placebo N _{LI} =364/ N _{PLA} =404	Quetiapine vs Lithium N _{QTP} =404/ N _{LI} =364
Analysis of time to relapse/recurrence of a mood event			
Hazard ratio [95% CI]	0.29 [0.23, 0.38]	0.46 [0.36, 0.59]	0.66 [0.49, 0.88]
p-value	<0.0001	<0.0001	0.005
Analysis of time to relapse/recurrence of a manic event			
Hazard ratio [95% CI]	0.29 [0.21, 0.40]	0.37 [0.27, 0.53]	0.78 [0.53, 1.16]
p-value	<0.0001	<0.0001	0.226
Analysis of time to relapse/recurrence of a depressed event			
Hazard ratio [95% CI]	0.30 [0.20, 0.44]	0.59 [0.42, 0.84]	0.54 [0.35, 0.84]
p-value	<0.0001	0.004	0.006

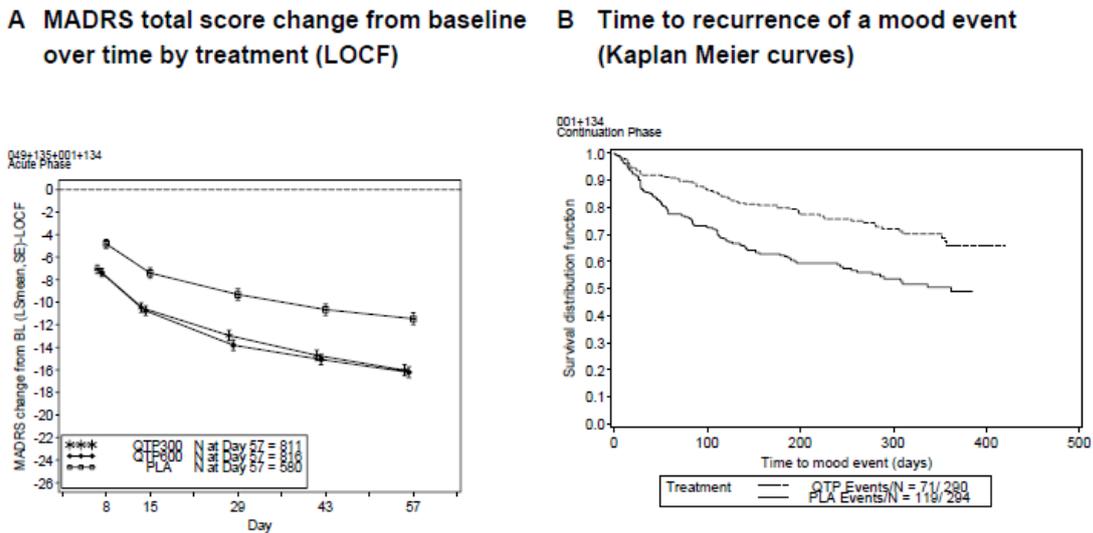
ITT Intent-to-treat. PLA Placebo. QTP Quetiapine. LI Lithium. VAL Valproate. N Number of patients in treatment group.

Bipolar depression

The safety and efficacy of quetiapine immediate release tablets 300 mg and 600 mg once daily for the treatment of bipolar depression was established in 4 similarly designed placebo controlled clinical trials (n=2461) over 8 weeks with 2 of these studies assessing maintenance of effect for up to 52 weeks. Patients met the DSM-IV criteria for bipolar I or II disorder, with or without rapid cycling courses. In the 8-week study period approximately 35% of patients met the criteria for bipolar II disorder.

Anti-depressant activity was assessed by the change from baseline for MADRS total score (primary endpoint), at 8 weeks (day 57). In all 4 studies quetiapine doses of 300 mg/day and 600 mg/day demonstrated clinical and statistical superiority to placebo in the treatment of depression at 8 weeks (refer Figure 3A). The anti-depressant effect of quetiapine was superior compared to placebo as early as day 8 (week 1) and was maintained through to week 8 (refer Figure 3A).

Figure 3 Treatment (A) and maintenance of effect (B) of Quetiapine Tablets in bipolar depression (Combined intention to treat population)



BL baseline. ITT Intention-to-treat. LOCF Last observation carried forward. LS Least squares. MADRS Montgomery-Asberg Depression Rating Scale. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine. SE standard error.

The magnitude of the anti-depressant effect, was supported by the secondary outcome variables [Hamilton Rating Scale for Depression (HAM-D) total score, the item analyses of the MADRS and HAM-D item 1 (depressed mood) score]. Response rates (defined as $\geq 50\%$ reduction in MADRS total score) and remission rates (defined as MADRS total score of 12 or less) were superior for quetiapine compared to placebo at week 8. The Clinical Global Impression – Severity of Illness (CGI-S) and Clinical Global Impression – Improvement (CGI-I), measures of the clinicians impression of the severity of the patients overall illness and improvement from baseline, were also assessed with quetiapine superior to placebo at week 8 in all 4 studies.

Alleviation of anxiety symptoms by quetiapine in all 4 studies was confirmed by a statistically superior Hamilton Rating Scale for Anxiety (HAM-A) total score change from baseline compared to placebo.

The change from baseline for total MADRS score for quetiapine vs placebo was statistically significant for patients with bipolar I or bipolar II disorder. Efficacy was also demonstrated to be independent of cycling frequency, gender, or age.

Quality of life assessments as measured by Q-LES-Q (Quality of Life Enjoyment and Satisfaction Scale) total score revealed superior improvement with quetiapine tablets 300 mg treatment and improvement was also seen with quetiapine tablets 600 mg compared to placebo.

Maintenance of the quetiapine effect in bipolar depression was demonstrated during the continuation phase with patients treated with quetiapine experiencing a significantly longer time to recurrence of any mood event (depression, mixed state or mania; defined as a MADRS score ≥ 20 or a YMRS score ≥ 16 ; initiation of an antipsychotic, anti-depressant, mood stabilizer

etc; hospitalization for symptoms of depression and/or mania/hypomania; discontinuation due to symptoms of depression and/or mania/hypomania), compared to placebo as shown in Figure 3B. Quetiapine patients had a lower risk of experiencing a mood event at weeks 26 and 52 compared to patients on placebo. Patients on quetiapine had a 49% less risk of experiencing a mood event compared with patients treated with placebo [HR 0.51 (95% CI 0.38, 0.69; $p < 0.001$)]. The risk of a mood event for quetiapine versus placebo was reduced by 41% for the 300 mg dose and by 55% for the 600 mg dose.

Quetiapine patients also had a lower risk of experiencing a depressed event at weeks 26 and 52 compared to patients on placebo. The analysis of time to a depressed event mirrored the overall mood event results with patients on quetiapine having a 57% less risk of experiencing a depressed event compared with patients treated with placebo (HR 0.43, 95% CI 0.30, 0.62, $p < 0.001$). The risk of a depressed event for quetiapine versus placebo was reduced by 52% for the 300 mg dose and by 61% for the 600 mg dose.

No increased risk for a manic or hypomanic event was observed. Quetiapine treatment of a depressed episode was also not associated with a switch to mania or hypomania.

Time to all cause discontinuation, including the composite mood event, was also examined with the Kaplan-Meier estimate of time to 50% all cause discontinuation being 311 days for quetiapine treatment, compared to 156 days for placebo treatment.

The maintenance of effect observed in patients treated with quetiapine was demonstrated to be independent of bipolar diagnosis (ie I or II), gender or age.

In the majority of studies in the acute phase statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10. There was also no increased risk of suicidal behaviour or ideation associated with quetiapine treatment for bipolar depression in either the acute or continuation phase.

Acute Mania

The efficacy of quetiapine immediate release tablets 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 CGI-Bipolar 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 800 mg per day. The mean last week median dose of quetiapine in responders was approximately 600 mg/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 800 mg per day. The mean last week median dose of quetiapine in responders was approximately 600 mg/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 immediate release tablets 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 tablets (75, 150, 300, 600 and 750 mg/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 750 mg/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 750 mg/day on a three times a day dosing schedule) and low (up to 250 mg/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 (450 mg/day on both twice a day and three times a day dosing schedules and 50 mg/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.

Children and adolescents (10 to 17 years of age)

Three clinical trials have been conducted with quetiapine immediate release tablets in children and adolescents; two short-term randomised placebo-controlled trials – a 6 week trial in schizophrenia (patients aged 13-17 years) and a 3 week trial in bipolar mania (patients aged 10 to 17 years) – and an open-label 26 week safety and tolerability trial (see **section 4.8 Adverse effects (Undesirable effects) – Clinical study experience**) which also assessed efficacy measures. The safety and efficacy of quetiapine in children and adolescents have not been assessed beyond these time periods.

Acute mania (monotherapy)

The efficacy of quetiapine in the treatment of acute manic episodes associated with bipolar I disorder in children and adolescents (10 to 17 years of age) was demonstrated in a 3-week, double-blind, placebo-controlled, multicentre trial. Patients who met DSM-IV diagnostic criteria for a manic episode were randomized into one of three treatment groups: Quetiapine Tablets 400 mg/day, Quetiapine Tablets 600 mg/day or placebo. Approximately 45% (n=124) of patients (n=277) had co-morbid attention deficit hyperactivity disorder (ADHD), with 59 (21%) of patients receiving concomitant psychostimulants (see section **4.5 Interactions with other medicines and other forms of interactions - Medications to manage attention deficit hyperactivity disorder (ADHD)**).

Study medication was initiated at 50 mg/day and on Day 2 increased to 100 mg/day. Subsequently, the dose was titrated to a target dose of 400 or 600 mg using increments of 100 mg/day, given two or three times daily. Results of the study demonstrated superior efficacy of quetiapine 400 mg/day and 600 mg/day compared with placebo (see Table 14).

Table 14 Summary of YMRS efficacy results (ITT population) for treatment of acute mania (monotherapy) in children/adolescents

YMRS endpoint	QTP 400mg vs PLA QTP N=93 / PLA N=89	QTP 600mg vs PLA QTP N=95 / PLA N=89
Total score – LS mean change from baseline to Day 21 (primary endpoint)	-14.25 vs -9.04; p<0.001	-15.60 vs -9.04; p<0.001
Response ^a (% patients) at Day 21	63 vs 37%; p=0.001	58 vs 37%; p=0.005
Remission ^b (% patients)	53 vs 30%; p=0.010	54 vs 30%; p=0.003

YMRS – Young Mania Rating Scale, ITT Intent-to-treat. LS – Least square, PLA Placebo. QTP Quetiapine. N Number of patients in treatment group, ^a ≥50% reduction for YMRS total score, ^b ≤12 YMRS total score

Schizophrenia

The efficacy of quetiapine in the treatment of schizophrenia in adolescents (13 to 17 years of age) was demonstrated in a 6-week, double-blind, placebo-controlled trial. Patients who met DSM-IV diagnostic criteria for schizophrenia were randomized into one of three treatment groups: Quetiapine 400 mg/day, quetiapine 800 mg/day, or placebo. Study medication was initiated at 50 mg/day and on Day 2 increased to 100 mg/per day. Subsequently, the dose was titrated to a target dose of 400 or 800 mg using increments of 100 mg/day, given two or three times daily. Results of the study demonstrated superior efficacy of quetiapine 400 mg/day and 800 mg/day compared to placebo (see Table 15).

Table 15 Summary of key efficacy results (ITT population) for treatment of schizophrenia in adolescents

Endpoint at Day 42	QTP 400mg vs PLA QTP N=73 / PLA N=73	QTP 800mg vs PLA QTP N=74 / PLA N=73
PANSS total score (MMRM) – LS mean change from baseline (primary endpoint)	-27.31 vs -19.15; p=0.043	-28.44 vs -19.15; p=0.009
PANSS response ^a (LOCF; % patients)	38.4 v 26.0; NS ^b	36.5 v 26.0; NS ^b
CGI - Global Improvement (LOCF; % patients with improvement)	49.3 v 27.4; p=0.009 ^c	52.7 v 27.4; p=0.014 ^c

MMRM - mixed model repeated measures; LOCF - last observation carried forward; ITT Intent-to-treat. PANSS – Positive and Negative Syndrome Scale; CGI - Clinical Global Impression; LS – Least square, PLA Placebo. QTP Quetiapine. N Number of patients in treatment group, ^a ≥30% reduction for PANSS total score; ^b Generalised estimating equation for statistics (N=220); ^c Generalised estimating equation for statistics (N=219)

5.2 PHARMACOKINETIC PROPERTIES

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 800 mg/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.

Excretion

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

Special patient populations

Use in the elderly

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

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/1.73m²), 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 section **4.2 Dose and method of administration - Hepatic impairment**).

Use in children and adolescents (10 to 17 years of age)

At steady-state the pharmacokinetics of the parent compound in children and adolescents (10-17 years of age) were similar to adults, while AUC and C_{max} of the active metabolite, norquetiapine, were higher in children and adolescents than in adults, 45% and 31%, respectively. However, when adjusted for weight AUC and C_{max} of the parent compound in children and adolescents were lower than in adults, 41% and 39%, respectively, while the pharmacokinetics of the metabolite, norquetiapine, was similar (see section **4.2 Dose and method of administration**).

5.3 PRECLINICAL SAFETY DATA

Acute toxicity studies

Quetiapine has low acute toxicity. Findings in mice (median lethal dose > 500 mg/kg PO; 100 mg/kg IP), rats (median lethal dose > 500 mg/kg PO; 100 mg/kg IP) and dogs (dose limit study 10-75 mg/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 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225 mg/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 section **4.8 Adverse effects (Undesirable 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.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Lactose monohydrate
- sodium starch glycollate (Type A)
- calcium hydrogen phosphate
- povidone
- microcrystalline cellulose
- magnesium stearate
- opadry complete film coating system 03B84929 pink (ARTG No.106711) [25 mg]
- opadry complete film coating system 03B52117 yellow (ARTG No.106712) [100 mg]
- hypromellose, macrogol 400 and titanium dioxide [200 mg, 300 mg]

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep in a dry place.

6.5 NATURE AND CONTENTS OF CONTAINER

Quetiapine APOTEX 25 mg

PVC/aluminium blister pack of 20 or 60 tablets; *AUST R 204157*.

Quetiapine APOTEX 100 mg

PVC/aluminium blister pack of 20 or 90 tablets; *AUST R 204158*.

Quetiapine APOTEX 200 mg

PVC/aluminium blister pack of 20 or 60 tablets; *AUST R 204159*.

Quetiapine APOTEX 300 mg

PVC/aluminium blister pack of 20, 60 or 100 tablets; *AUST R 204160*.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

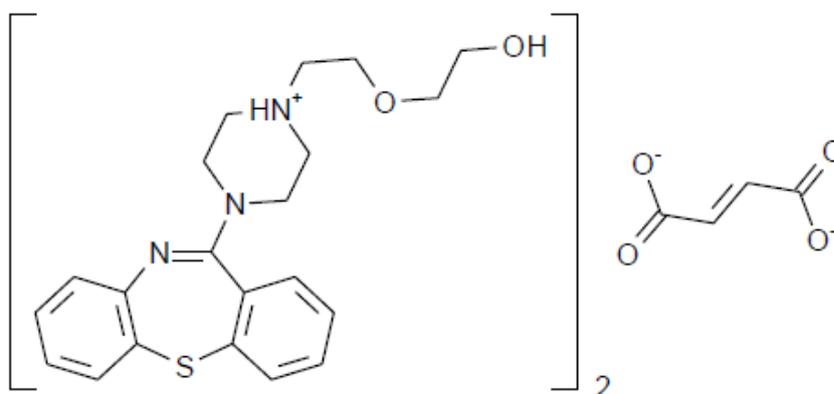
6.7 PHYSICOCHEMICAL PROPERTIES

Quetiapine fumarate is white to off white powder. It is a weak acid (pKa 3.3, 6.8) which exhibits moderate pH dependent solubility 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 moderate aqueous solubility at 25°C and exhibits suitable tableting properties when combined with appropriate excipients.

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

Chemical structure



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

Quetiapine fumarate has a molecular formula of $C_{46}H_{54}N_6O_8S_2$ and a molecular weight of 883.1.

CAS number

111974-72-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only Medicine (S4)

8 SPONSOR

Accord Healthcare Pty Ltd
 Level 24, 570 Bourke Street
 Melbourne, VIC, 3000

DISTRIBUTOR

Apotex Pty Ltd
 16 Giffnock Avenue
 Macquarie Park NSW 2113
 Australia

Tel: +61 2 8877 8333

Web: www1.apotex.com/au**9 DATE OF FIRST APPROVAL**

02, April, 2014

10 DATE OF REVISION

6 March, 2019

Summary table of changes

Section Changed	Summary of new information
Various	New PI format
2	AAN included for Excipients with known effect
4.4	New precautions included related to Severe Cutaneous Adverse Reactions, Venous thromboembolism, Neutropenia and Agranulocytosis, Hepatic, Dependence/tolerance, Dependence/tolerance, Sleep apnoea, Anti-cholinergic (muscarinic) effects and Use in the elderly. Precautions for Extrapramidal symptoms (EPS) and Metabolic factors updated
4.5	Interactions with medication having anti-cholinergic (muscarinic) effects included
4.8	Other adverse drug reactions and post marketing experience sections updated
4.9	Overdose section updated

6.1	AAN (Lactose monohydrate) for Lactose included
8	Updated sponsor details
Various	Changed trade name to Quetiapine APOTEX
8	Added distributor information