NEW ZEALAND DATA SHEET

QUETAPEL

1. Product Name

Quetapel, 25 mg, 100 mg, 200 mg and 300 mg tablets.

2. Qualitative and Quantitative Composition

Each tablet contains 25 mg, 100 mg, 200 mg or 300 mg of quetiapine (as quetiapine fumarate).

Excipient with known effect: Lactose

Allergen Declaration: Contains Sugars as lactose.

Each Quetapel 25 mg tablet contains 5 mg lactose.

Each Quetapel 100 mg tablet contains 18 mg lactose.

Each Quetapel 200 mg tablet contains 36 mg lactose.

Each Quetapel 300 mg tablet contains 54 mg lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Quetapel 25 mg is presented as a peach coloured, round, biconvex, film-coated tablet containing quetiapine fumarate delivering a dose of 25 mg of quetiapine free base. The tablets are 5 mm in diameter and are engraved ‘Q’ on one side.

Quetapel 100 mg is presented as a yellow coloured, round, biconvex, film-coated tablet containing quetiapine fumarate delivering a dose of 100 mg of quetiapine free base. The tablets are 8.5 mm in diameter and are engraved ‘Q’ over ‘100’ on one side.

Quetapel 200 mg is presented as a white coloured, round, biconvex, film-coated tablet containing quetiapine fumarate delivering a dose of 200 mg of quetiapine free base. The tablets are 11 mm in diameter and are engraved ‘Q’ over ’200’ on one side.

Quetapel 300 mg is presented as a white coloured capsule-shaped (19 mm x 7.5 mm), film-coated tablet containing quetiapine fumarate delivering a dose of 300 mg of quetiapine free base. Each film-coated tablet is engraved with ‘Q’ breakline ‘300’ on one side. The opposing side is plain except for the breakline.

Do not halve Quetapel 25 mg, 100 mg or 200 mg Tablets.

4. Clinical Particulars

4.1 Therapeutic indications

Quetiapine is indicated in adults only, for the treatment of:

- Acute and chronic psychoses, including schizophrenia.
- Bipolar Disorder including:
    - treatment of manic episodes satisfying DSM-IV criteria for mania associated with bipolar disorder
    - treatment of depressive episodes associated with bipolar disorder
    - maintenance treatment of bipolar I disorder, in combination with a mood stabiliser, for the prevention of recurrence of manic, depressive or mixed episodes.

4.2 Dose and method of administration

Adults

For the treatment of acute and chronic psychoses, including schizophrenia

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

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 range of 300 - 450 mg/day. However, this may be adjusted, depending on the clinical response and tolerability of the individual patient, within the range 150 to 750 mg/day.

For the treatment of manic episodes associated with bipolar disorder

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

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). 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.

For the treatment of depressive episodes associated with bipolar disorder

Quetiapine should be administered once daily at bedtime, with or without food.

The usual dose is 300 mg/day. The 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). Quetiapine can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Antidepressant efficacy was demonstrated with quetiapine at 300 mg and 600 mg, however no additional benefit was seen in the 600 mg group during short term treatment (see sections 4.8 and 5.1).

For the maintenance treatment of bipolar I disorder in combination with mood stabilisers

Patients who have responded to quetiapine in combination therapy with a mood stabiliser for acute treatment of bipolar disorder should continue on quetiapine therapy at the same dose.

The quetiapine dose can be re-adjusted depending on clinical response and tolerability of the individual patient.

Efficacy was demonstrated with quetiapine (administered twice daily totalling 400 mg to 800 mg a day) as combination therapy with a mood stabiliser.

Special populations

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.

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 daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

Paediatric

Quetiapine is not indicated for use in children and adolescents below 18 years of age. Data from placebo-controlled clinical trials are detailed within the data sheet (see section 4.4, 4.8, and 5.1).

4.3 Contraindications

Quetiapine is contraindicated in patients who have a known hypersensitivity to quetiapine or any component of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV protease inhibitors, azole antifungal agents, erythromycin, clarithromycin and nefazodone is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Suicide / suicidal thoughts or clinical worsening

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. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. Consideration should be given to given to changing the therapeutic regimen, including possibly discontinuing the medicine, 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. Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depressive disorder. The

same precautions observed when treating patients with major depressive disorder should therefore be observed when treating patients with other psychiatric disorders.

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

Symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania and mania have been reported in adults, adolescents and children being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. 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 non-psychiatric) 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 medicine 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 medicines. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine, and preventative measures undertaken.

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 medicines). Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period.

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 it's a α_1-adrenergic antagonist properties. Syncope has been commonly reported (see section 4.8). Orthostatic hypotension, dizziness and syncope may lead to falls (see section 4.8). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Dysphagia

Oesophageal dysmotility and aspiration have been reported with antipsychotic medicine use. Although a causal relationship with aspiration pneumonia has not been established, quetiapine and other antipsychotic medicines should be used with caution in patients at risk for aspiration pneumonia (e.g. elderly patients).

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medicines that decrease intestinal motility and/or may not report symptoms of constipation.

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). 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.

Tardive dyskinesia

In placebo-controlled clinical trials in 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. This predicts that quetiapine has less potential than typical antipsychotic agents to induce tardive dyskinesia in schizophrenia and bipolar mania patients.

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.

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medicines including quetiapine. 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).

Extrapyramidal symptoms (EPS)

In short-term, placebo-controlled clinical trials in adult patients with bipolar depression, the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients (see section 4.8 for rates of EPS observed in all indications and ages).

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.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment including quetiapine (see section 4.8). 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.

Serotonin syndrome

Concomitant administration of quetiapine and other serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Body temperature regulation

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

QT prolongation

In clinical trials quetiapine was not associated with a persistent increase in absolute QT_c intervals. However, in post-marketing experience there were cases reported of QT prolongation with overdose (see section 4.9), in patients with concomitant illness, and in patients taking medicines known to cause electrolyte imbalance or increase QT interval. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Particularly in the elderly, the use of quetiapine should be avoided in combination with neuroleptics and medicines that are known to prolong QT_c including Class Ia antiarrhythmics (e.g. disopyramide) or Class III antiarrhythmics (e.g. amiodarone, sotalol), antipsychotic medicines (e.g. ziprasidone, chlorpromazine, haloperidol), antibiotics (e.g. moxifloxacin, erythromycin), or any other class medicines known to prolong the QT_c interval (e.g. citalopram, pentamidine, methadone). Quetiapine should also be avoided in circumstances that may increase the risk of occurrence of torsades de pointes and/or sudden death, including (1) a history of cardiac arrhythmias such as bradycardia; (2) hypokalaemia or hypomagnesemia; (3) concomitant use of other medicines that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval.

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience (see section 4.8). In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.

Neutropenia and agranulocytosis

Severe neutropenia (< 0.5 x 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), history of medicine 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 x 10^9/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x 10^9/L) (see section 4.8).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Acute Generalized Ezanthematous Pustulosis (AGEP), Erythema multiforme (EM) and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life threatening adverse reactions that have been reported during quetiapine exposure. SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia, or neutrophilia. Discontinue quetiapine if severe cutaneous adverse reactions occur.

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea and vomiting 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).

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, medicine-seeking behaviour), particularly if they have a history of alcohol or drug abuse.

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). 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 baseline 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 antidiabetic treatment despite discontinuation of the suspect medicine.

Lipids

Increases in triglycerides and cholesterol, and decreases in fasting HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). 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 medicines 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 the post marketing experience, however a causal relationship has not been established. 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 section 4.5), gallstones and alcohol consumption.

Sleep Apnoea

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

Somnolence

Quetiapine treatment has been associated with somnolence and related symptoms such as sedation. In clinical trials for the treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Bipolar depression patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from the onset of somnolence, or until symptoms improve. Treatment discontinuation may need to be considered.

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anticholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medicines having anticholinergic effects, and in setting of overdose. Quetiapine should be used with caution in patients receiving medicines 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 4.5**,** 4.8, 4.9 and 5.1).

Hepatic enzyme inducers

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

CYP3A4 inhibitors

During concomitant administration of medicines which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence of this, lower doses of quetiapine should be used. Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients (see section 4.5).

Special populations

Children and adolescents (10 to 17 years of age)

Quetiapine is not indicated for use in children and adolescents below 18 years of age.

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 warnings and precautions for use that appear for adults should be considered for paediatrics. Additionally, changes in blood pressure and thyroid function tests and increases in weight and prolactin levels have been observed and should be managed as clinically appropriate (see section 4.8).

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

Hepatic disorders / liver failure

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

Hepatic failure, including fatalities, has also 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).

Safety experience in elderly patients with dementia-related psychosis

Quetiapine is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increase of cerebrovascular adverse events has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

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 medicine-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 medicine-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.

In two 10-week placebo-controlled quetiapine studies in elderly patients (n=710; mean age: 83 years; range: 56-99 years) with dementia-related psychosis, the incidence of death in quetiapine-treated patients was 5.5% vs. 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Lactose monohydrate

Quetapel contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the lapp lactase deficiency, or glucose-galactose malabsorprion should not take this medicine.

Interference with Laboratory Tests

Leukopenia and/or neutropentia

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 medicine induced leukopenia and/or neutropenia. Occasionally, eosinophilia has been observed (see section 4.8).

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).

Lipids

Increases in triglyceride levels and total cholesterol (predominantly LDL cholesterol) have been observed during treatment with quetiapine. Decreases in fasting HDL cholesterol have also been observed (see section 4.8).

Thyroid hormone levels

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T_4 – 3.4% for quetiapine versus 0.6% for placebo; free T_4 – 0.7% for quetiapine versus 0.1% for placebo; total T_3 – 0.54% for quetiapine versus 0.0% for placebo and free T_3 – 0.2% for quetiapine versus 0.0% for placebo. The incidence of shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T_4 and TSH. As supported by the literature, these changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first 6 weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with reversal of the effects on total and free T_4, irrespective of the duration of treatment (see section 4.8).

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 Interaction with other medicines and other forms of interaction

Antipsychotic and other centrally acting medicines

Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicines and alcohol. The association with somnolence and related symptoms such as sedation is particularly important in those with risk factors for or a history of sleep apnoea.

Quetiapine should be used with caution in combination with serotonergic medicinal products, such as monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

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). CYP2D6 and CYP2C9 are also involved.

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

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

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

Ketoconazole

In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of quetiapine given before and during treatment with ketoconazole, co-administration of ketoconazole (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. It should be noted that the recommended maximum daily dose of quetiapine is 750 mg/day, for the treatment of acute and chronic psychoses including schizophrenia, and 800 mg/day for the treatment of manic episodes associated with bipolar disorder.

Co-administration of quetiapine (250 mg three times a day) with phenytoin (100 mg three times a day; another microsomal enzyme inducer) also caused increases in the clearance of quetiapine by 5-fold. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

Cardiovascular medicines

Caution should be exercised when quetiapine is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval (see section 4.4).

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

Anticholinergic (muscarinic) effects

Caution should be exercised treating patients receiving other medicines having anti-cholinergic (muscarinic) effects (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy – Category C

Quetiapine may have adverse metabolic effects, including diabetes mellitus, during pregnancy (see section 4.4).

The safety and efficacy of quetiapine during human pregnancy have not been established. Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks and the administered dose and duration of treatment should be as low and as short as possible.

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

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).

Breastfeeding

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 metabolites was higher in milk than in plasma. Women who are breastfeeding should therefore be advised to avoid breast-feeding while taking quetiapine.

Fertility

The effects of quetiapine on human fertility have not been assessed.

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 may interfere with activities requiring mental alertness, impair judgement, thinking or motor skills. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

4.8 Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine are headache, somnolence, dizziness, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum

triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

The incidences of ADRs associated with quetiapine therapy, are tabulated below according to the format recommended by the Council for International Organisations of Medical Sciences (CIOMS III Working Group; 1995).

Table 1: Incidences of ADRs associated with quetiapine therapy

Frequency	System Organ Class	Event
Very Common (≥ 10%)	Gastrointestinal disorders	Dry mouth
	General disorders and administration site conditions	Withdrawal (discontinuation) symptoms[1,10]
	Investigations	Elevations in serum triglyceride levels[1,11] Elevations in total cholesterol (predominantly LDL cholesterol)[1,12] Decreases in HDL cholesterol[18] Weight gain[3] Decreased haemoglobin[19]
	Nervous system disorders	Dizziness[1,5,17] Somnolence[2,17] Extrapyramidal symptoms[1,16] Headache
Common (≥ 1% - < 10%)	Blood and lymphatic system disorders	Leukopenia[1,24]
	Cardiac disorders	Tachycardia[1,5] Palpitations[20]
	Eye disorders	Vision blurred
	Gastrointestinal disorders	Constipation Dyspepsia Vomiting[22]
	General disorders and administration site conditions	Mild asthenia Peripheral oedema Irritability Pyrexia
	Investigations	Elevations in serum alanine aminotransferase (ALT)[4] Elevations in gamma-GT levels[4] Neutrophil count decreased[1,7] Eosinophils increased[23] Blood glucose increased to hyperglycaemic level[1,8] Elevations in serum prolactin[15] Decreases in Total T_4[21] Decreases in Free T_4[21] Decreases in Total T_3[21] Increases in TSH[21]
	Nervous system disorders	Dysarthria
	Metabolism and nutrition disorders	Increased appetite
	Respiratory, thoracic, and mediastinal disorders	Dyspnoea[20]
	Vascular disorders	Orthostatic hypotension[1,5,17]
	Psychiatric disorders	Abnormal dreams and nightmares
Uncommon (≥ 0.1% - < 1%)	Cardiac disorders	Bradycardia[25]

Frequency	System Organ Class	Event
	Gastrointestinal disorders	Dysphagia[1,9]
	Immune system disorders	Hypersensitivity Angioedema
	Investigations	Elevations in serum aspartate aminotransferase (AST)[4] Platelet count decreased[14] Decreases in Free T_3[21]
	Nervous system disorders	Seizure[1] Restless legs syndrome Tardive dyskinesia[1] Syncope[1,5,17] Confusional state
	Respiratory, thoracic and mediastinal disorders	Rhinitis
	Renal and urinary disorders	Urinary retention
Rare (0.01% - < 0.1%)	General disorders and administration site conditions	Neuroleptic malignant syndrome[1] Hypothermia
	Hepatobiliary disorders	Hepatitis (with or without jaundice)
	Investigations	Elevations in blood creatine phosphokinase (not associated with neuroleptic malignant syndrome)[13] Agranulocytosis[26]
	Psychiatric disorders	Somnambulism (sleepwalking) and other related behaviours including sleep-related eating disorder
	Reproductive system and breast disorders	Priapism Galactorrhoea
	Gastrointestinal disorders	Intestinal obstruction/Ileus
Very Rare (< 0.01%)	Immune system disorders	Anaphylactic reaction[6]
	Musculoskeletal and connective tissue disorders	Rhabdomyolysis
Not known	General disorders and administration site conditions	Neonatal withdrawal[27]
	Skin and subcutaneous disorders	Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP) Cutaneous vasculitis Erythema multiforme (EM)
	Cardiac disorders	Cardiomyopathy and myocarditis

1. See section 4.4.

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

3. Based on ≥ 7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

4. Asymptomatic elevations (shift from normal to > 3 x ULN at any time) in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.

5. As with other antipsychotics with alpha$_1$ adrenergic blocking activity, quetiapine may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.

6. The inclusion of anaphylactic reaction is based on post-marketing reports.

7. In all short-term placebo-controlled monotherapy trials among patients with a baseline neutrophil count ≥ 1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count < 1.5 x 10^9/L, was 1.9% in patients treated with quetiapine, compared to 1.3% in placebo-treated patients. The incidence ≥ 0.5 - < 1.0 x 10^9/L was 0.2% in patients treated with quetiapine and 0.2% in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment-emergent neutrophil count < 1.0 x 10^9/L, among patients with a baseline neutrophil count ≥ 1.5 x 10^9/L, the incidence of at least one occurrence of neutrophil count < 0.5 x 10^9/L was 0.21% in patients treated with quetiapine and 0% in placebo treated patients.

8. Fasting blood glucose ≥ 126 mg/dL (≥7.0 mmol/L) or a non fasting blood glucose ≥ 200 mg/dL (≥11.1 mmol/L) on at least one occasion.

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

10. In acute placebo-controlled, monotherapy clinical trials, 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 the individual adverse events (e.g., insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability) did not exceed 6.7% in any treatment group and usually resolved after 1 week post-discontinuation.

11. Triglycerides ≥ 200 mg/dL (≥2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥1.694 mmol/L) (patients < 18 years of age) on at least one occasion.

12. Cholesterol ≥ 240 mg/dL (≥6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥5.172 mmol/L) (patients < 18 years of age) on at least one occasion.

13. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

14. Platelets ≤ 100 x 10^9/L on at least one occasion.

15. Prolactin levels (patients ≥ 18 years of age): > 20 mcg/L males; > 30 mcg/L females at any time.

16. See text below.

17. May lead to falls.

18. HDL cholesterol: < 40 mg/dL (1.025 mmol/L) males; < 50 mg/dL (1.282 mmol/L) females at any time.

19. Decreased haemoglobin to ≤ 13 g/dL (8.07 mmol/L) males, ≤ 12 g/dL (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 ≤ 13 g/dL (8.07 mmol/L) males, ≤ 12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 8.3% of quetiapine patients compared to 6.2% of placebo patients.

20. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.

21. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as < 0.8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.

22. Based on the increased rate of vomiting in elderly patients (≥ 65 years of age).

23. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as > 1 x 10^9 cells/L at any time.

24. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as < 3 x 10^9 cells/L at any time.

25. 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.

26. Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia (< 0.5 x. 10^9/L) and infection.

27. See section 4.6.

Extrapyramidal symptoms

The following clinical trials (monotherapy and combination therapy) in adult patients included treatment with immediate release quetiapine and modified release quetiapine.

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania, the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). In short-term, placebo-controlled clinical trials in bipolar depression, the aggregated incidence of extrapyramidal symptoms 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.

Diabetes mellitus

Exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis, have occurred very rarely with quetiapine therapy. The causal association with quetiapine has not been established (see section 4.4).

Thyroid levels

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were: total T_4: 3.4% for quetiapine versus 0.6% for placebo; free T_4: 0.7% for quetiapine versus 0.1% for placebo; were total T_3: 0.54% for quetiapine versus 0.0% for placebo and free T_3: 0.2% for quetiapine versus 0.0% for placebo. The incidence shifts in TSH was 3.2% for quetiapine versus 2.7% for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0.0% for both quetiapine and placebo and 0.1% for quetiapine versus 0.0% for placebo for shifts in T_4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. In nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. In eight patients, where TBG was measured, levels of TBG were unchanged.

QT prolongation

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported very rarely with the use of neuroleptics and are considered class effects.

Special populations

Children and adolescents (10 to 17 years of age)

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

Table 2: ADRs that occur in a higher frequency in children and adolescent patients

Frequency	System Organ Class	Event
Very Common (≥ 10%)	Metabolism and nutrition disorders	Increased appetite
	Investigations	Elevations in prolactin[1] Increases in blood pressure[2] Weight gain[3]
	Gastrointestinal disorders	Vomiting[2]
Common (≥ 1% - < 10%)	Respiratory, thoracic and mediastinal disorders	Rhinitis[2]
	Nervous system disorders	Syncope[2]

1. Prolactin levels (patients < 18 years of age): > 20 mcg/L (> 869.56 pmol/L) males; > 26 mcg/L (> 1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level > 100 mcg/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 in children and adolescents (10 to 17 years of age)

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. Twenty-one percent of quetiapine-treated patients and 7% of placebo-treated patients gained $\geq$ 7% of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine-treated patients and 0% of placebo-treated patients gained $\geq$ 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 increase in body weight was 4.4 kg. Forty-five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks, an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

In one 8-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar depression, in which efficacy was not established, the mean increase in body weight was 1.4 kg in the modified release quetiapine group and 0.6 kg in the placebo group. 13.7% of modified release quetiapine-treated patients and 6.8% of placebo-treated patients gained ≥ 7% of their body weight.

Extrapyramidal symptoms in children and adolescent population (10 to 17 years of age)

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

In a short-term placebo-controlled monotherapy trial in children and adolescent patients (10 to 17 years of age) with bipolar depression in which efficacy was not established, the aggregated incidence of extrapyramidal symptoms was 1.1% for modified release quetiapine and 0.0% for placebo.

Post-marketing experience

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, 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).

Other adverse events reported since market introduction, which were temporally related to quetiapine therapy, but not necessarily causally related, include: cardiomyopathy, myocarditis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatraemia, cerebrovascular accident and Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine. Most patients who overdosed reported no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine alone.

In post-marketing experience, there have been very rare reports of overdose with 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 increased risk of the effects of overdose (see section 4.4).

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

Management of overdose

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple medicine 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 beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade).

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antipsychotics, ATC code: N05AH04

Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to $Dopamine_2$ receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effects (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin $5HT_{1A}$ receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at $5HT_{1A}$ sites by norquetiapine may contribute to quetiapine's therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes which may explain anti-cholinergic (muscarinic) effects.

Pharmacodynamic effects

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 dopamine D_2 receptor blockade.

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

Clinical efficacy and safety

Clinical trials have demonstrated that quetiapine is effective when given twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours. This is further supported by the data from a positron emission tomography (PET) study which identified that for quetiapine, $5HT_2$ and $Dopamine_2$ receptor occupancy are maintained for up to 12 hours. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

Schizophrenia

In clinical trials, quetiapine has been shown to be effective in the treatment of both positive and negative symptoms of schizophrenia. In comparative clinical trials, quetiapine has been shown to be as effective as standard antipsychotic agents such as chlorpromazine and haloperidol.

Adolescents (13 to 17 years of age)

Quetiapine is not indicated for use in children and adolescents below 18 years of age. The efficacy of quetiapine in the treatment of schizophrenia in adolescents (13-17 years of age) was demonstrated in a 6 week, double-blind, placebo-controlled trial. Patients who met DSM-IV diagnostic criteria for schizophrenia were randomised into one of three treatment groups: quetiapine 400 mg/day (n = 73), quetiapine 800 mg/day (n = 74), or placebo (n = 75). Study medicine was initiated at 50 mg/day and on day 2 increased to 100 mg/per day. Subsequently, the dose was titrated to the target dose of 400 or 800 mg using increments of 100 mg/day, given two or three times daily. The primary efficacy variable was the mean change from baseline in total Positive and Negative Syndrome Scale.

Results of the study demonstrated efficacy of quetiapine 400 mg/day and 800 mg/day compared to placebo. Greater efficacy of the 800 mg dose compared with the 400 mg dose has not been established.

Bipolar mania

In clinical trials, quetiapine has been shown to be effective as monotherapy or as adjunct therapy in reducing manic symptoms in patients with bipolar mania. Efficacy has been demonstrated up to 12 weeks in the monotherapy setting. In the adjunct setting, there are no efficacy data beyond 6 weeks. The mean last week median dose of quetiapine in responders, was approximately 600 mg and approximately 85% of the responders were in the dose range of 400 to 800 mg/day.

Children and adolescents (10 to 17 years of age)

Quetiapine is not indicated for use in children and adolescents below 18 years of age. 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 randomised into one of three treatment groups: quetiapine 400 mg/day (n = 95), quetiapine 600 mg/day (n = 98), or placebo (n = 91). Study medicine 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. The primary efficacy variable was the mean change from baseline in total YMRS score.

Results of the study demonstrated superior efficacy of quetiapine 400 mg/day and 600 mg/day compared with placebo. Greater efficacy of the 600 mg dose compared with the 400 mg dose has not been established.

Bipolar depression

In four clinical trials, which included patients who are bipolar I, bipolar II and patients with and without rapid cycling courses, quetiapine has been shown to be effective in patients with bipolar depression at doses of 300 and 600 mg/day, however, no additional benefit was seen with the 600 mg dose during short-term treatment.

In all four studies, quetiapine was superior to placebo in reduction of Montgomery-Asberg Depression Scale (MADRS) total score. The antidepressant effect of quetiapine was significant at Day 8 (Week 1) and was maintained through the end of the studies (Week 8). Treatment with either quetiapine 300 or 600 mg at bedtime reduced depressive symptoms and anxiety symptoms in patients with bipolar depression. There were fewer episodes of treatment emergent mania with either dose of quetiapine than with placebo.

In 3 out of 4 studies, for the 300 mg and 600 mg dose group, statistically significant improvements over placebo were seen in reductions in suicidal thinking as measured by MADRS item 10 and in 2 out of 3 studies, for the 300 mg dose group, overall quality of life and satisfaction related to various areas of functioning, as measured using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).

In two bipolar depression clinical trials with quetiapine in adult patients, maintenance of antidepressant efficacy was established. These trials included an 8-week placebo-controlled acute phase, followed by a placebo-controlled continuation phase of at least 26 weeks but up to 52-weeks in duration. Patients were required to be stable at the end of the acute phase in order to be in the randomized into continuation phase. In both trials, quetiapine was superior to placebo in increasing the time to recurrence of any mood event (depressed, mixed or manic). The risk reduction from the pooled trials was 49%. 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.

Bipolar maintenance

The efficacy of quetiapine in the maintenance treatment of bipolar disorder was established in 2 placebo-controlled trials in 1326 patients who met DSM-IV criteria for bipolar I disorder. The trials included patients whose most recent mood episode was manic, depressed, or mixed, with or without psychotic features. In the open-label phase, patients were required to be stabilised on quetiapine in combination with a mood stabiliser (lithium or valproate) for a minimum of 12 weeks in order to be randomised. In the randomisation phase, patients either continued treatment with quetiapine (administered twice daily totalling 400 to 800 mg per day) in combination with mood stabiliser (lithium or valproate) or received placebo in combination with mood stabiliser (lithium or valproate) for up to 104 weeks.

In each study, quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), the primary endpoint. The risk reductions were 70%, 67% and 74% for mood, manic and depressive events.

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

Similarly, maintenance treatment with quetiapine was superior to placebo in increasing the time to recurrence of a manic event. Patients on quetiapine also had a lower risk of experiencing a manic event prior to week 28 and week 52 compared to patients on placebo.

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

Clinical safety – suicide / suicidal thoughts or clinical worsening

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

In these trials of patients with schizophrenia, the incidence of suicide related events was 1.4% (3/212) for quetiapine and 1.6% (1/62) for placebo in patients 18-24 years of age, 0.8% (13/1663) for quetiapine and 1.1% (5/463) for placebo in patients $\geq$ 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 (5/463) 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 (see section 4.4).

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 ≥ 25 years of age. There has been one trial conducted in patients 10-17 years of age in which efficacy was not established. The incidence of suicide related events was 1.0% (1/92) for quetiapine and 0% (0/100) for placebo. In this study there were two additional events in two patients that occurred during an extended post-treatment follow-up phase of the study; one of these patients was on quetiapine at the time of the event (see section 4.4).

Cataracts / lens opacities

In a clinical trial to evaluate the cataractogenic potential of quetiapine versus risperidone in the long-term treatment of patients with schizophrenia or schizoaffective disorder, quetiapine at doses of 200-800 mg/day was non-inferior for the 2-year event rate of increase in LOCS II (Lens Opacities Classification System II) lens opacity grade (Nuclear opalescence, Cortical, and Posterior subcapsular standards for LOCS II) to risperidone at doses of 2 to 8 mg/day for patients with at least 21 months of exposure (see section 5.3).

5.2 Pharmacokinetic properties

Absorption and distribution

Quetiapine is well absorbed and extensively metabolised following oral administration. The bioavailability of quetiapine is not significantly affected by administration with food. 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 elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively.

Biotransformation

Quetiapine is extensively metabolised by the liver with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. Approximately 73% of the radioactivity is excreted in the urine and 21% in the faeces. The mean plasma clearance of quetiapine is reduced by approximately 25% in subjects with hepatic impairment (stable alcoholic cirrhosis). 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).

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*. *In vitro* CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these *in vitro* results, it is unlikely that coadministration of quetiapine with other medicines will result in clinically significant medicine inhibition of cytochrome P450 mediated metabolism of the other medicine.

Elimination

Norquetiapine is primarily formed and eliminated via CYP3A4.

Linearity/non-linearity

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

Special populations

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.

Renal impairment and hepatic impairment

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 mL/min/1.73m^2) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5% excreted in the urine.

Children and adolescents (10 to 17 years of age)

At steady-state the pharmacokinetics of the parent compound quetiapine, 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 Cmax 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.

5.3 Preclinical safety data

Acute toxicity studies

Quetiapine has low acute toxicity. Findings in mice and rats after oral (500 mg/kg) or intraperitoneal (100 mg/kg) dosing were typical of an effective neuroleptic agent and included decreased motor activity, ptosis, loss of righting reflex, 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 medicine 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 and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey.

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

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

Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in Cynomolgus monkeys dosed up to 225 mg/kg/day, nor in rodents. Monitoring in clinical studies did not reveal medicine-related corneal opacities in man (see section 5.1).

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

Carcinogenicity studies

In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia.

In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.

Reproduction studies

Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction.

Quetiapine had no teratogenic effects.

Mutagenicity studies

Genetic toxicity studies with quetiapine show that it is not a mutagen or clastogen.

6. Pharmaceutical Particulars

6.1 List of excipients

- Microcrystalline cellulose
- Sodium starch glycolate
- Lactose monohydrate
- Povidone
- Calcium hydrogen phosphate dihydrate
- Magnesium stearate
- Hypromellose
- Macrogol
- Titanium dioxide (E 171)

Quetapel 25 mg also contains Iron Oxide Red CI77491 (E 172).
Quetapel 100 mg also contains Iron Oxide Yellow CI77492 (E 172) and Talc.
Quetapel 200 mg and 300 mg also contain Polysorbate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Quetapel 25 mg, 100 mg, 200 mg, 300 mg: 3 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Quetapel 25 mg, 100 mg, 200 mg & 300 mg tablets are available in foil blister packs containing 90 tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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AUCKLAND

www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

15 March 2007

10. Date of Revision of the Text

08 April 2026

Summary table of changes

Section	Summary of new information
Throughout	Minor editorial changes
2	Relocation of allergen information from section 6.1 Addition of lactose quantity.
4.4	Updated 'Suicide/suicidal thoughts or clinical worsening', 'Concomitant cardiovascular illness', 'Dysphagia', 'Seizures', 'Tardive dyskinesia', 'Extrapyramidal symptoms (EPS)', 'QT prolongation', 'Cardiomyopathy and myocarditis', 'Neutropenia and agranulocytosis', 'Lipids', 'Metabolic factors', 'Pancreatitis', 'Severe Cutaneous Adverse Reactions', 'Hepatic disorders/liver failure', and 'Safety experience in elderly patients with dementia-related psychosis' sections Addition of 'Venous Thromboembolism', 'orthostatic hypotension', 'Serotonin syndrome', 'Body temperature regulation', 'Dependence/tolerance', 'Sleep Apnoea', 'Hepatic enzyme inducers', 'CYP3A4 inhibitors', 'Lactose monohydrate', and 'Interference with Laboratory Tests' sections Removal of 'Misuse and abuse' section
4.5	Addition of 'Antipsychotic and other centrally acting medicines' section Removal of 'Medicines to manage ADHD', and 'Methadone and tricyclic antidepressants' section
4.6	Updated 'Pregnancy', 'Breastfeeding' and 'Fertility' sections
4.7	Updated Effects on ability to drive and use machines
4.8	Addition of Table headers Updated Table 1 notes. Clarification of side effects such as Elevations in blood creatine phosphokinase, Somnambulism and other related behaviours. Addition of headache, and cardiac disorders (Cardiomyopathy and myocarditis) as an ADR.

	Addition of ‘Post-marketing experience’ Updated ADR reporting website
4.9	Updated ‘Management of overdose’ section
6.1	Relocation of allergen information to section 2