1. NAME OF THE MEDICINAL PRODUCT

XYTAL-100 (QUETIAPINE TABLETS USP 100 MG)

2. QUALITATIVE AND QUANTITATIVECOMPOSITION

Each film coated tablet contains:
Quetiapine fumarate USP
Eq. to Quetiapine 100 mg
Excipients Q.S
Colour: Yellow Oxide of iron

3. PHARMACEUTICAL FORM

Oral Film coated tablets

4. Clinical particulars

4.1 Therapeutic indications

Treatment of schizophrenia

The antipsychotic efficacy of Xytal-100 was established in short-term (6 weeks) controlled trials of adults and one 6-week trial in adolescents (13-17 years) schizophrenic in patients.

The effectiveness of Xytal-100 in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials.

Therefore, the physician who elects to use Xytal-100 for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct to lithium or divalproex

The efficacy of Xytal-100 in acute bipolar mania was established in two 12-week monotherapy trials in adults, in one 3-week adjunctive trial in adults, and in one 3-week monotherapy trial in paediatric patients (10-17 years).

Treatment of depressive episodes associated with bipolar disorder

The efficacy of Xytal-100 was established in two identical 8-week randomised, placebo-controlled double-blind clinical studies that included either bipolar I or bipolar II patients with and without rapid cycling courses (See 'Pharmacodynamic properties, clinical efficacy').

Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

The efficacy of Xytal-100 as adjunct maintenance therapy to lithium or divalproex was established in 2 identical randomized placebo-controlled double-blind studies in patients with Bipolar I Disorder (See 'Clinical Efficacy').

The physician who elects to use Xytal-100 for extended periods in Bipolar Disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See 'Posology and Method of Administration').

Special Considerations in Treating Paediatric Schizophrenia and Bipolar I Disorder

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 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.

Prevention of recurrence in patients with bipolar disorder, in patients whose manic or depressive episode has responded to quetiapine treatment.

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4.2 Posology and method of administration

Route of Administration: Oral

Posology and Method of Administration

Schizophrenia

Adults

Xytal-100 should be administered twice daily, with or without food. Xytal-100 should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for Xytal-100 would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended.

Antipsychotic efficacy was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of Xytal-100. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety and efficacy doses above 800 mg/day have not been evaluated in clinical trials.

Adolescents (13-17 years)

Xytal-100 should be administered twice daily. However, based on response and tolerability Xytal-100 may be administered three times daily where needed.

The total daily dose for the initial 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 recommended dose range of 400 mg/day to 800 mg/day based on response and tolerability.

Dosage adjustments should be in increments of no greater than 100 mg/day.

Efficacy was demonstrated with Xytal-100 at both 400 mg and 800 mg;
however, no additional benefit was seen in the 800 mg group.

Maintenance Treatment

While there is no body of evidence available to answer the question of how long the patient treated with Xytal-100 should remain on it, the effectiveness of maintenance treatment is well established for many other antipsychotic drugs. It is recommended that responding patients be continued on Xytal-100, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off Xytal-100, titration of Xytal-100 is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off Xytal-100 for more than one week, the

initial titration schedule should be followed.

Acute manic episodes associated with bipolar I disorder

Adults

Xytal-100 should be administered twice daily, with or without food.

As monotherapy or as adjunct therapy to mood stabilizers (lithium or divalproex), 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 per day by Day 6 should be in increments of no greater than 200 mg per day.

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

Children and Adolescents (10 to 17 years)

Xytal-100 should be administered twice daily. However, based on response and tolerability Xytal-100 may be administered three times daily where needed. The total daily dose for the initial 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 recommended dose range of 400 to 600 mg/day based on response and tolerability. Dosage adjustments should be in increments of no greater than 100 mg/day.

Efficacy was demonstrated with Xytal-100 at both 400 mg and 600 mg; however, no additional benefit was seen in the 600 mg group.

Depressive episodes associated with bipolar disorder

Xytal-100 should be administered once daily at bedtime, with or without food.

Xytal-100 should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). Xytal-100 can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Antidepressant efficacy was demonstrated with Xytal-100 at 300 mg and 600 mg however no additional benefit was seen in the 600 mg group. (See 'Undesirable Effects and Clinical Efficacy')

Maintenance treatment of bipolar I disorder as adjunct therapy to lithium or divalproex

Adults

Maintenance of efficacy in Bipolar I Disorder was demonstrated with Xytal-100 (administered twice daily totalling 400 to 800 mg per day) as adjunct therapy to lithium or divalproex. Generally, in the maintenance
phase, patients continued on the sa me dose on which they were stabilized during the stabilization phase (See 'Clinical Efficacy').

Children and Adolescents (10 to 17 years)

The effectiveness of Xytal-100 for longer than 3 weeks has not been evaluated in controlled clinical trials of children and adolescents. While there is no body of evidence available to answer the question of how long the patient treated with Xytal-100 should be maintained, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Preventing recurrence in bipolar disorder

For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is
used for maintenance therapy.

Elderly

As with other antipsychotics, Xytal-100 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 30-50% in elderly subjects when compared to younger patients.

Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Paediatric Use

In general, the adverse reactions observed in children and adolescents during the clinical trials were similar to those in the adult population with few exceptions. Increases in systolic and diastolic blood pressure occurred in children and adolescents and did not occur in adults. Orthostatic

hypotension occurred more frequently in adults (4-7%) compared to children and adolescents (<1%).

Schizophrenia

The efficacy and safety of Xytal-100 in the treatment of schizophrenia in adolescents aged 13 to 17 years were demonstrated in one six week, double-blind, placebo-controlled trial. Safety and effectiveness of Xytal-100 in paediatric patients less than 13 years of age with schizophrenia have not been established.

Maintenance

The safety and effectiveness of Xytal-100 in the maintenance treatment of bipolar disorder has not been established in paediatric patients less than 18 years of age. The safety and effectiveness of Xytal-100 in the

maintenance treatment of schizophrenia has not been established in any patient population, including paediatric patients.

Bipolar Mania

The efficacy and safety of Xytal-100 in the treatment of mania in children and adolescents ages 10 to 17 years with Bipolar I disorder was demonstrated in a 3-week, double-blind, placebo-controlled, multicentre

trial. Safety and effectiveness of Xytal-100 in paediatric patients less than 10 years of age with bipolar mania have not been established.

Bipolar Depression

Safety and effectiveness of Xytal-100 in paediatric patients less than 18 years of age with bipolar depression have not been established.

Some differences in the pharmacokinetics of quetiapine were noted between children/adolescents (10 to 17 years of age) and adults. When adjusted for weight, the AUC and Cmax of quetiapine were 41% and 39%

lower, respectively, in children and adolescents compared to adults. The pharmacokinetics of the active metabolite, norquetiapine, were similar between children/adolescents and adults after adjusting for weight.

Renal impairment

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment

Quetiapine is extensively metabolised by the liver. Therefore, Xytal-100 should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with known hepatic impairment should be started with 25 mg/day. The dosage should be increased daily with increments of 25-50 mg/day until an effective dosage, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients 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 'Interactions with other medicaments and other forms of interaction).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening

Depression in bipolar disorder is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery. 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.

Patients with a history of suicide-related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts,

and should receive careful monitoring during treatment. An FDA metaanalysis of placebo-controlled clinical trials of antidepressant drugs in approximately 4400 children and adolescents and 77000 adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in children, adolescents, and young adult patients less than 25 years old. This meta-analysis did not include trials involving quetiapine (see 'Pharmacodynamic properties').

Neutropenia and agranulocytosis

Severe neutropenia (neutrophil count <0.5 X 109/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) and history of drug induced 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 109/L. These patients should be observed for signs and symptoms of infection and neutrophil count followed (until they exceed 1.5 X 109/L). (see 'Undesirable effects').

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. Assessment of the relationship between atypical antipsychotics 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 this confounder, 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. 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 HDL have been observed in clinical trials with quetiapine (See 'Undesirable effects'). 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. Changes in these parameters 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 'Special Warnings & Precautions for use – Lipids'), gallstones, and alcohol consumption.

Tardive dyskinesia and Extrapyramidal symptoms (EPS)

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic drugs 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 *'Undesirable Effects'*).

In placebo-controlled clinical trials of adult patients with schizophrenia and bipolar mania the incidence of extrapyramidal symptoms 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. 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 '*Undesirable effects'*).

Concomitant illness

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension, especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs.

In patients who have a history of or are at risk for sleep apnea, and are receiving concomitant

central nervous system (CNS) depressants, quetiapine should be used with caution.

Dysphagia

Dysphagia (See *'Undesirable effects'*) and aspiration have been reported with quetiapine. Although a causal relationship with aspiration pneumonia has not been established, quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (See *'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.

Seizures

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (See '*Undesirable effects'*).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (See *'Undesirable effect'*). 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.

QT Prolongation

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose. (See '*Overdose'*). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed with medicines known to increase QTc interval, and concomitant neuroleptics, especially for patients with increased risk of QT prolongation, ie. the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (See '*Interactions with other medicaments and other forms of interaction'*).

Cardiomyopathy and Myocarditis

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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens - Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema multiforme (EM) 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 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 drugs including quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (See *'Undesirable effects'*).

Misuse and abuse

Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.

4.5 Interaction with other medicinal products and other forms of interaction

Interactions

See also '*Interactions with other medicaments and other forms of interaction'*. 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 is used concomitantly with a hepatic enzyme inducer. 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.

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

Although not all adverse reactions that have been identified in the adult patients have been observed in clinical trials with quetiapine in children and adolescent patients, the same special warnings and special precautions for use that appear above 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 *'Undesirable effects'*). 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 to 17 years of age).

Elderly patients with dem entia

Quetiapine is not approved for the treatment of dementia-related psychosis. In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. However in two 10-week placebo-controlled quetiapine studies in the same patient population (n=710); mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died of 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.

Anticholinergic (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 medications having anticholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anticholinergic (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 *'Interactions with other medicinal products', 'Undesirable effects',*
'Pharmacodynamic properties, Mechanism of Action', and 'Overdose'.)

Lactose

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

Additional information

Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (See '*Undesirable effects'* and *'Pharmacodynamic properties'*). The data showed an additive effect at week 3. Interactions with other medicaments and other forms of interaction Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting
drugs and alcohol. Caution should be exercised when quetiapine is used concomitantly with drugs known to cause electrolyte imbalance or to increase QT interval (See '*Special warnings and precautions for use').* Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see Section '*Special Warning and Precautions for Use'*). Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy. The pharmacokinetics of lithium were not altered when co-administered with quetiapine.
The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.
The pharmacokinetics of quetiapine was not significantly altered following coadministration with the antipsychotics risperidone or haloperidol. However co-administration of quetiapine and thioridazine caused increases in the clearance of quetiapine.
Quetiapine did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. However, 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 600 to 800 mg/day depending on indication (see '*Posology and Method of Administration'*).
Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit risk assessment for an individual patient. Co-administration of quetiapine and with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of quetiapine. Increased doses of quetiapine may be required to maintain control of psychotic symptoms in patients co-administered quetiapine and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc). The dose of quetiapine may need to be reduced if phenytoin or carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).
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

4.6 Pregnancy and Lactation

The safety and efficacy of quetiapine during human pregnancy have not yet 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. There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. 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

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine (≥10%) are 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 Organizations of Medical Sciences (CIOMS III Working Group; 1995). The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000).

Blood and lymphatic system disorders
Common: Leucopenia [1, 25]
Uncommon: Thrombocytopenia
Unknown: Neutropenia

Immune system disorders
Uncommon: Hypersensitivity
Very rare: Anaphylactic reaction [6]

Endocrine disorders
Common: Hyperprolactinaemia [16]
Very rare: Inappropriate antidiuretic hormone secretion

Metabolism and nutritional disorders
Common: Increased appetite
Uncommon: Hyponatraemia [29]
Very rare: Diabetes Mellitus [1, 5,6]

Psychiatric disorders
Common: Abnormal dreams and nightmares Suicidal ideation and suicidal behaviour [25]
Rare: Somnambulism and other related events

Nervous system disorders
Very Common: Dizziness [1, 4, 17], somnolence [2, 17], headache, extrapyramidal symptoms [1, 13]
Common: Dysarthria
Uncommon: Seizure [1], restless legs syndrome, tardive dyskinesia [1], syncope [1, 4, 17]

Cardiac disorders
Common: Tachycardia [1, 4,] palpitations [21]
Uncommon: Bradycardia [26]

Eye disorders
Common: Vision blurred

Vascular disorders
Common: Orthostatic hypotension [1, 4, 17]

Rare: Venous thromboembolism [1]

Respiratory, thoracic and mediastinal disorder
Common: Dyspnea [21]
Uncommon: Rhinitis, Sleep apnoea [30]

Renal and urinary disorders
Uncommon: Urinary retention

Gastrointestinal disorders
Very common: Dry mouth
Common: Constipation, dyspepsia, vomiting [23]
Uncommon: Dysphagia [1, 8]
Rare: Intestinal obstruction/Ileus

Hepato-biliary disorders
Rare: Jaundice, hepatitis [6]

Skin and subcutaneous tissue disorders
Very rare: Angioedema [6,] Stevens-Johnson syndrome [6]
Not known Drug reaction with eosinophilia and systemic symptoms (DRESS)
Acute Generalized Exanthematous Pustulosis (AGEP)
Erythema multiforme (EM)

Musculoskeletal and connective tissue disorders
Very rare: Rhabdomyolysis

Reproductive system and breast disorders
Uncommon Sexual dysfunction
Rare: Priapism, galactorrhoea, breast swelling, menstrual disorder

General disorders and administration site conditions
Very common Withdrawal (discontinuation) symptoms [1,10]
Common: Mild asthenia, peripheral oedema, irritability, pyrexia
Rare: Neuroleptic malignant syndrome 1, hypothermia
Not known: Neonatal withdrawal [28]

Investigations
Very common Elevations in serum triglyceride levels [1, 11], elevations in total cholesterol (predominantly LDL cholesterol) [1, 12], decreases in HDL cholesterol [1, 18], weight gain [9,] decreased haemoglobin [19]
Common: Elevations in serum alanine aminotransferase (ALT) [3],elevations in gamma-GT levels [3], decreased neutrophil count [1], eosinophils increased [24], blood glucose increased to hyperglycaemic levels [1, 7], QT prolongation [1, 13, 20], elevations in serum prolactin 16, decreases in Total T_4 [22], decreases in Free T_4 [22], decreases in Total T_3[22], increases in TSH [22]
Uncommon: Elevations in serum aspartate aminotransferase (AST) [3], platelet count decreased [14], decreases in free T_3 [22]
Rare Elevations in blood creatine phosphokinase [15], agranulocytosis 27

1. See '*Special Warnings and Precautions for use'*.
2. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of Quetiapine.
3. Asymptomatic elevations (shift from normal to ≥3X 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.
4. As with other antipsychotics with alpha1 adrenergic blocking activity, Quetiapine may

commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (See '*Special Warnings and Precautions for use'*).
5. Exacerbation of pre-existing diabetes has been reported in very rare cases.
6. Calculation of Frequency for these ADR's have been taken from post-marketing data only.
7. Fasting blood glucose ≥126mg/dL (≥7.0 mmol/L) or a non-fasting blood glucose ≥200mg/dL (≥11.1 mmol/L) on at least one occasion.
8. An increase in the rate of dysphagia with Quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
9. Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
10. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
11. Triglycerides ≥200mg/dL (≥2.258 mmol/L) on at least one occasion.
12. Cholesterol ≥240mg/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. An increase in LDL cholesterol of ≥30 mg/dL (≥0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥1.07 mmol/L).
13. See text below.
14. Platelets ≤100 x 109/L on at least one occasion
15. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
16. Prolactin levels (patients >18 years of age): >20 µg/L (>869.56 pmol/L) males; >30 µg/L (>1304.34 pmol/L) females at any time.
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 males, ≤12 g/dL 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 males, ≤12 g/dL females on at least one occasion occurred in 8.3% of quetiapine patients compared to 6.2% of placebo patients.
20. Incidence of patients who have a QTc shift from <450 msec to ≥450 msec with a ≥30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.
21. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
22. 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 <0.8 x LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.
23. Based upon the increased rate of vomiting in elderly patients (≥65 years of age).
24. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as ≥1 x 109 cells/L at any time.
25. Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤3X109cells/L at any time.
26. 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.
27. Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia (<0.5 x 109/L) and infection.
28. See '*Pregnancy and lactation'*.
29. Shift from >132 mmol/L to <132 mmol/L on at least one occasion.
30. Atypical antipsychotic drugs, such as quetiapine, have been associated with cases of sleep apnoea, with or without concomitant weight gain. In patients who have a history of or are at risk for sleep apnoea, Quetiapine should be prescribed with caution.

Extrapyramidal Symptoms

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 (eg, 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.

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 T4: 3.4 % for quetiapine versus 0.6 % for placebo; free T4: 0.7%

for quetiapine versus 0.1% for placebo; total T3: 0.54 % for quetiapine versus 0.0% for placebo and free T3: 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 T3 and TSH was 0.0 % for both quetiapine and placebo and 0.1% for quetiapine versus 0.0 % for placebo for shifts in T4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic

hypothyroidism. The reduction in total and free T4 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 T4, irrespective of the duration of treatment. In eight patients, where TBG was measured, levels of TBG were unchanged.

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 adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

The frequencies of adverse events are ranked according to the following: Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000) and very rare (<1/10,000).
Metabolism and nutritional disorders
Very common: Increased appetite

Investigations
Very common: Elevations in prolactin [1], increases in blood pressure [2]

Nervous system disorders
Common: Syncope [2]

General disorders and administration site conditions
Common: Irritability [3]

Respiratory, thoracic, and mediastinal disorders
Common: Rhinitis [2]

Gastrointestinal disorders
Very common: Vomiting [2]

(1) Prolactin levels (patients <18 years of age): >20 µg/L (>869.56 pmol/L) males; >26 µg/L (>1130.428 pmol/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 Institute of Health criteria) or increases >20mmHg 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.
(3) Note: The frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.

Weight Gain in 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. Twenty one percent 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.
Twelve percent 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 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 Quetiapine XR group and 0.6 kg in the placebo group. 13.7 % of Quetiapine XR-treated patients and 6.8% of placebo-treated patients gained ≥ 7 % of their body weight.
Extrapyramidal Symptoms in Children and Adolescent Population
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 (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 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 (10-17 years of age) with bipolar depression in which efficacy was not established, the aggregated incidence of extrapyramidal symptoms was 1.1% for Quetiapine XR and 0.0% for placebo.

4.9 Overdose

Fatal outcome has been reported in clinical trials following an acute overdose at 13.6 grams, and in post-marketing on doses as low as 6 grams of Quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 grams. In post marketing experience, there have been very rare reports of overdose of Quetiapine alone, resulting in death or coma or QT-prolongation.
Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (See *'Special Warnings and Precautions for Use – Concomitant 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 anticholinergic 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. In this context, published reports in the setting of anti-cholinergic symptoms describe a reversal of severe CNS effects, including coma and delirium, with
administration of intravenous physostigmine (1-2 mg), under continuous ECG monitoring.
In cases of quetiapine overdose refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group : Antipsychotics
Therapeutic classification : N05A H04
Pharmacodynamic properties
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 (5HT2) and dopamine D1 and D2 receptors. It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to dopamine D2 receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Quetiapine. Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin 5HT1A receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to

Quetiapine's
therapeutic efficacy as an antidepressant. Quetiapine and norquetiapine 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 sever al 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 electro physiologically, and elevates dopamine metabolite concentrations, a neurochemical index of dopamine D2receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike standard antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2 receptor super sensitivity 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 A10 mesolimbic but not the A9 nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration.

Clinical efficacy

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, 5HT2 and dopamine 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.

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)

The efficacy of Quetiapine in the treatment of schizophrenia in adolescents (13–17 years of age) was demonstrated in a six week, double-blind, placebo-controlled trial. Patients who met DSM-IV diagnostic criteria for schizophrenia were randomized into one of three treatment groups: Quetiapine 400mg/day (n = 73), Quetiapine 800 mg/day (n = 74), or placebo (n = 75). Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/per day (divided and given two or three times per day).

Subsequently, the dose was titrated to the target dose of 400 mg/day or 800 mg/day using increments of 100 mg/day, divided and given two or three times daily. The primary efficacy variable was the mean change from baseline in total Positive and Negative Syndrome Scale (PANSS).

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. The mean last week median dose of Quetiapine in responders, was approximately 600 mg/day 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)

The efficacy of Quetiapine in the acute treatment of 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 400 mg/day (n = 95), Quetiapine 600 mg/day (n = 98), or placebo (n = 91). Study medication was initiated at 50 mg/day and on day 2 increased to 100 mg/day (divided doses given two or three times daily). Subsequently, the dose was titrated to a target dose of 400 mg/day or 600 mg/day using increments of 100 mg/day, given in divided doses 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.

<u>Bipolar Depression</u>

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 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 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 3 studies, for the 300 mg dose group, overall quality of life and satisfaction related to various areas of functioning, as measured using the Q-LES-Q (SF).

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.

<u>Preventing Recurrence in Maintenance Treatment of Bipolar Disorder</u>

The efficacy of Quetiapine in the monotherapy treatment for recurrence prevention was established in 1 placebo-controlled trial in 1226 patients who met DSM-IV criteria for Bipolar I Disorder. The trial included patients whose most recent mood episode was manic, mixed, or depressive with or without psychotic features. In the open-label phase, patients were required to be stabilised on Quetiapine for a minimum of 4 weeks in order
to be randomized. In the randomization phase, patients either continued treatment with Quetiapine (300 to 800 mg per day: average dose 546 mg per day) or were to receive lithium or placebo for up to 104 weeks.

Quetiapine was superior to placebo in increasing the time to recurrence of any mood event

(manic, mixed, or depressive), the primary endpoint. The risk reductions were 74%, 73%, and 75% for mood, manic and depressive events, respectively.
The efficacy of Quetiapine in the combination treatment for recurrence prevention was established in 2 placebo-controlled trial in 1326 patients who met DSM-IV criteria for Bipolar I Disorder. The trials included patients whose most recent mood episode was manic, mixed, or depressive, with or without psychotic features. In the open-label phase, patients were required to be stabilized on Quetiapine in combination with mood stabilizer (lithium or valproate) for a minimum of 12 weeks in order to be randomized. In the randomization phase, patients either continued treatment with Quetiapine
(400 to 800 mg per day average dose 507 per day) in combination with mood stabilizer or received placebo in combination with mood stabilizer for up to 104 weeks. Quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressive), the
primary endpoint. The risk reductions were 70%, 67%, and 74% for mood, manic and depressive events, respectively.

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 ≥ 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 ≥ 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 ≥ 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 Special warnings and special precautions for use).

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of Quetiapine (200-800 mg/day) versus risperidone (2-8 mg) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in Quetiapine (4%) compared with risperidone
(10%), for patients with at least 21 months of exposure.

5.2 Pharmacokinetic properties

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.
The pharmacokinetics of quetiapine and norquetiapine are linear across the approved

dosing range. The kinetics of quetiapine do not differ between men and women.
The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.
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. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.
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 quetiapine plasma clearance decreases with approx. 25% in persons with known hepatic impairment (stable alcoholcirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (See *'Posology & Method of Administration'*).
In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.
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 co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug.
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 Cmax 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 (See '*Dosing and Administration'*).

5.3 Preclinical safety data

There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research: In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts.
In an embryofoetal toxicity study in rabbits the foetal incidence of carpal/ tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.
In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy,

protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related
to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core	Coating
Dibasic Calcium Phosphate Microcrystalline Cellulose Lactose monohydrate Sodium Starch Glycolate (Type A) Povidone K 30 Magnesium stearate Croscarmellose sodium	Colorezy white 17F580001 Yellow Oxide of iron (only in 100mg)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months for the date of manufacturing.

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container<and special equipment for use, administration or implantation>

3 X 10 Tablets Alu-Alu Blister Pack

6.6 Special precautions for disposal <and other handling>

There are no special storage precautions. Any unused product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT/MANUFACTURER

STALLION LABORATORIES PVT. LTD.
C-1B, 305/2, 3, 4 & 5, G.I.D.C.,
KERALA (BAVLA),
DIST.: AHMEDABAD,
GUJARAT, INDIA.