PROFESSIONAL INFORMATION:

SCHEDULING STATUS:

S5

1. NAME OF THE MEDICINE:

QUETIAPINE 50 TEVA film-coated tablets

QUETIAPINE 200 TEVA film-coated tablets

QUETIAPINE 300 TEVA film-coated tablets

QUETIAPINE 400 TEVA film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

QUETIAPINE 50 TEVA: Each film-coated tablet contains quetiapine fumarate equivalent to 50 mg of quetiapine.

QUETIAPINE 200 TEVA: Each film-coated tablet contains quetiapine fumarate equivalent to 200 mg of quetiapine.

QUETIAPINE 300 TEVA: Each film-coated tablet contains quetiapine fumarate equivalent to 300 mg of quetiapine.

QUETIAPINE 400 TEVA: Each film-coated tablet contains quetiapine fumarate equivalent to 400 mg of quetiapine.

Sugar free.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Prolonged-release film-coated tablets.

QUETIAPINE 50 TEVA: Brown, biconvex, oblong, film-coated tablets with debossing 'Q50' on one side.

QUETIAPINE 200 TEVA: Yellow, biconvex, oblong, film-coated tablets with debossing 'Q200' on one side.

QUETIAPINE 300 TEVA: Light yellow, biconvex, oblong, film-coated tablets with debossing 'Q300' on one side.

QUETIAPINE 400 TEVA: White, biconvex, oblong, film-coated tablets with debossing 'Q400' on one side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

QUETIAPINE TEVA is indicated for the treatment of:

- Schizophrenia
- Preventing relapse in stable schizophrenic patients who have been maintained on QUETIAPINE TEVA
- Bipolar disorder including:
    - Manic episodes associated with bipolar disorder
    - Depressive episodes associated with bipolar disorder
    - Preventing recurrence in the maintenance treatment of bipolar disorder (manic, mixed or depressive episodes) as monotherapy or in combination with mood stabilisers
- Major depressive disorder
- Preventing relapse in stable major depressive disorder patients who have been maintained on QUETIAPINE TEVA.

4.2 Posology and method of administration:

Posology:

Adults:

For the treatment of schizophrenia:

The daily dose at the start of therapy is 300 mg on Day 1 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400 to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of manic episodes associated with bipolar disorder:

The daily dose at the start of therapy is 300 mg on Day 1 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400 to 800 mg per day, depending on the clinical response and tolerability of the patient.

For the treatment of depressive episodes associated with bipolar disorder:

QUETIAPINE TEVA should be administered once daily in the evening.

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

Antidepressant efficacy as demonstrated with QUETIAPINE TEVA at 300 mg and 600 mg, however no additional benefit was seen in the 600 mg group during short-term treatment.

For preventing recurrence in maintenance treatment of bipolar disorder:

Patients who have responded to QUETIAPINE TEVA in combination therapy to a mood stabiliser (lithium or valproate) for acute treatment of bipolar disorder should continue on QUETIAPINE TEVA therapy at the same dose. The QUETIAPINE TEVA dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 400 to 800 mg per day. Patients who have responded to QUETIAPINE TEVA for acute treatment of bipolar disorder should continue on QUETIAPINE TEVA therapy at the same dosing regimen. QUETIAPINE TEVA dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 to 800 mg per day.

For the treatment of major depressive disorder:

QUETIAPINE TEVA should be administered once daily in the evening.

Initial dosing should begin at 50 mg on Day l and 2, increased to 150 mg on Day 3 and 4. Further adjustments can.be made upwards or downwards within the recommended dose range of 50 to 300 mg depending upon the clinical response and tolerability of the patient.

For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient.

Switching from Quetiapine immediate release tablets:

For more convenient dosing, patients who are currently being treated with divided doses of Quetiapine immediate release dosage form (Quetiapine tablets) may be switched to QUETIAPINE TEVA at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Elderly*:*

QUETIAPINE TEVA should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of QUETIAPINE TEVA may need to be slower, and the daily therapeutic dose lower than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30 to 50 % in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg per day. The dose can be increased in increments of 50 mg per day to an effective dose, depending on the clinical response and tolerance of the individual patient.

In elderly patients with major depressive disorder initial dosing should begin at 50 mg on days 1 to 3, the dose can be increased to 100 mg on Day 4, 150 mg on Day 8 and then up to 300 mg depending on clinical response and tolerability.

Children and adolescents:

The safety and efficacy of QUETIAPINE TEVA have not been evaluated in children and adolescents.

Renal and hepatic impairment:

Renal impairment:

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolised by the liver. Therefore, QUETIAPINE TEVA 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 50 mg per day. The dose can be increased in increments of 50 mg per day to an effective dose, depending on the clinical response and tolerability of the individual patient.

Method of administration:

QUETIAPINE TEVA should be administered once daily, with or without food.

The tablets should be swallowed whole and not split, chewed or crushed.

4.3 Contraindications:

- hypersensitivity to quetiapine or to any of the excipients listed in **section 6.1**
- concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal medicines, erythromycin, clarithromycin and nefazodone, is contraindicated (see **section 4.5**)
- pregnancy and lactation (see **section 4.6**)
- safety and efficacy in children and adolescents have not been demonstrated
- advanced liver and renal dysfunction, as safety has not been demonstrated.

4.4 Special warnings and precautions for use:

As QUETIAPINE TEVA has several indications, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see **section 5.1**).

Suicide/suicidal thoughts or clinical worsening:

Depression 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.

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

Other psychiatric conditions for which QUETIAPINE TEVA 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 episodes.
The same precautions observed when treating patients with major depressive episodes 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.

Close supervision of patients and in particular those at high risk should accompany medicine therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

Reports have shown in shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3,0 % vs. 0 %, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2,1 % (3/144) for quetiapine and 1,3 % (1/75) for placebo. Reports from a population-based retrospective study of quetiapine for the treatment of

patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm during use of quetiapine with other antidepressants.

Metabolic Risk:

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycaemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see also **section 4.8**).

Tardive dyskinesia and Extrapyramidal symptoms:

There is a potential for QUETIAPINE TEVA to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, discontinuation of QUETIAPINE TEVA should be considered.

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 TEVA has less potential than typical antipsychotic medicines 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 **section 4.8**).

Somnolence and dizziness:

QUETIAPINE TEVA treatment has been associated with somnolence and related symptoms, such as sedation (see **section 4.8**). In clinical trials for treatment of patients with bipolar depression and major depressive disorder, onset was usually within the first 3 days of treatment and was predominantly of mild to

moderate intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic Hypotension:

QUETIAPINE TEVA treatment has been associated with orthostatic hypotension and related dizziness (see **section 4.8**) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

QUETIAPINE TEVA should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

Sleep apnoea syndrome:

Sleep apnoea syndrome has been reported in patients using QUETIAPINE TEVA. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, QUETIAPINE TEVA should be used with caution.

Seizures:

Caution is recommended when treating patients with a history of seizures (see **section 4.8**).

Neuroleptic Malignant Syndrome:

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including QUETIAPINE TEVA (see **section 4.8**). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, QUETIAPINE TEVA should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis:

Severe neutropenia (neutrophil count <0,5 X 10^9/L) without infection has been uncommonly reported in quetiapine clinical trials. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine, as contained in QUETIAPINE TEVA, during clinical trials as well as post-marketing reports. Most cases of severe neutropenia have occurred within the first two months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of medicine 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 TEVA should be discontinued in patients with a neutrophil count <1,0 x 10^9/L. 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 5.1**).

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat) at any time during QUETIAPINE TEVA therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

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 anti-cholinergic effects when QUETIAPINE TEVA is used at recommended doses, when used concomitantly with other medicines having anti-cholinergic effects, and in the setting of overdose. QUETIAPINE TEVA should be used with caution in patients receiving medicines having anti-cholinergic (muscarinic) effects. QUETIAPINE TEVA 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** and **4.8**).

Interactions:

Concomitant use of QUETIAPINE TEVA with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of QUETIAPINE TEVA therapy. In patients receiving a hepatic enzyme inducer, initiation of QUETIAPINE TEVA treatment should only occur if the medical practitioner considers that the benefits of QUETIAPINE TEVA outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate). See also **section 4.5**.

Weight:

Weight gain has been reported in patients who have been treated with QUETIAPINE TEVA and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see **sections 4.8** and **5.1**).

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 TEVA.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics such as QUETIAPINE TEVA, 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 such as QUETIAPINE TEVA, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as QUETIAPINE TEVA, should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as QUETIAPINE TEVA, was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

Lipids:

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been reported (see **section 4.8**). Lipid changes should be managed as clinically appropriate.

QT prolongation:

In clinical trials quetiapine was not associated with a persistent increase in absolute QTc intervals. In post-marketing, QT prolongation was reported with QUETIAPINE TEVA at the therapeutic doses (see **section 4.8**) and in overdose (see **section 4.9**). Caution should be exercised when QUETIAPINE TEVA is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when QUETIAPINE TEVA is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see **section 4.5**).

Cardiomyopathy and myocarditis:

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience. Treatment with QUETIAPINE TEVA 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 Generalised Exanthematous Pustulosis (AGEP), Erythema Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) which can be life threatening or fatal have been reported very rarely with QUETIAPINE TEVA treatment.

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. Most of these reactions occurred within 4 weeks after initiation of quetiapine therapy, some DRESS reactions occurred within 6 weeks after initiation of QUETIAPINE TEVA therapy. If signs and symptoms suggestive of these severe skin reactions appear, QUETIAPINE TEVA should be withdrawn immediately and alternative treatment should be considered.

Withdrawal:

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of QUETIAPINE TEVA. Gradual withdrawal over a period of at least one to two weeks is advisable (see **section 4.8**).

Elderly patients with dementia-related psychosis:

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

In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56 to 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 from a variety of causes that were consistent with expectations for this population.

Elderly patients with Parkinson's disease (PD)/parkinsonism:

A population-based retrospective study of quetiapine for the treatment of patients with MDD, showed an increased risk of death during use of quetiapine in patients aged > 65 years. This association was not present when patients with PD were removed from the analysis. Caution should be exercised if QUETIAPINE TEVA is prescribed to elderly patients with Parkinson's disease.

Dysphagia:

Dysphagia (see **section 4.8**) has been reported with QUETIAPINE TEVA. QUETIAPINE TEVA 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 TEVA (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 medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE):

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

Pancreatitis:

Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides, gallstones and alcohol consumption.

Misuse and abuse:

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

Paediatric population:

QUETIAPINE TEVA is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults (see **section 4.8**), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment with QUETIAPINE TEVA on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania and bipolar depression (see **section 4.8**).

4.5. Interaction with other medicines and other forms of interaction:

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

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

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 TEVA with CYP3A4 inhibitors is contraindicated (see **section 4.3**). It is also not recommended to consume grapefruit juice while on quetiapine therapy.

Reports from 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, which could affect the efficacy of QUETIAPINE TEVA therapy. Co-administration of QUETIAPINE TEVA and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450 %. In patients receiving a hepatic enzyme inducer, initiation of QUETIAPINE TEVA treatment should only occur if the medical practitioner considers that the benefits of QUETIAPINE TEVA outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see **section 4.4**).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of QUETIAPINE TEVA and thioridazine caused an increased clearance of quetiapine with approximately 70 %.

Concomitant administration of clarithromycin and atypical antipsychotics that are predominantly metabolised through the CYP3A4 pathway, for example quetiapine, cariprazine, and aripiprazole may result in an increase in plasma levels of these antipsychotics as a result of inhibition which may present a potential for serious adverse reactions.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.

The pharmacokinetics of lithium were not altered when co-administered with QUETIAPINE TEVA.

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered.

Caution should be exercised when QUETIAPINE TEVA is used concomitantly with medicines known to cause electrolyte imbalance or to increase QT interval (see **sections 4.4** and **4.8**).

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

4.6 Fertility, pregnancy and lactation:

Pregnancy:

Animal studies have shown reproductive toxicity (see **section 5.3**).

QUETIAPINE TEVA is contraindicated during pregnancy and lactation, as safety has not been demonstrated (see **section 4.3**).

***Breastfeeding*:**

Women who are breastfeeding should be advised to avoid breastfeeding while taking QUETIAPINE TEVA.

Fertility:

The effects of quetiapine as contained in QUETIAPINE TEVA on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans (see **section 5.3** preclinical data).

4.7 Effects on ability to drive and use machines:

Given its primary central nervous system effects, QUETIAPINE TEVA 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:

Blood and lymphatic system disorders:	
Frequent	Decreased haemoglobin[22,] leucopenia [1, 28], decreased neutrophil count, increased eosinophils [27]
Less frequent	Neutropenia[1], thrombocytopenia, anaemia, decreased platelet count [13], agranulocytosis [26]
Immune system disorders:	
Less frequent	Hypersensitivity (including allergic skin reactions), anaphylactic reaction[5]
Endocrine disorders:	
Frequent	Hyperprolactinemia[15], decreases in total T_4[24], decreases in free T_4[24], decreases in total T_3[24], increases in TSH [24]
Less frequent	Decreases in free T_3[24], hypothyroidism[21], inappropriate antidiuretic hormone secretion
Metabolism and nutritional disorders:	
Frequent	Elevations in serum triglyceride levels [10,30] elevations in total cholesterol (predominantly LDL cholesterol) [11,30], decreases in HDL cholesterol [17, 30],

	weight gain [8,30], increased appetite, blood glucose increased to hyperglycaemic levels[6,30]
Less frequent	Hyponatraemia [19], diabetes mellitus [1,5], exacerbation of pre-existing diabetes, metabolic syndrome[29]
Psychiatric disorders:	
Frequent	Abnormal dreams and nightmares, suicidal ideation and suicidal behaviour[20]
Less frequent	Somnambulism and related reactions such as sleep talking and sleep related eating disorder
Nervous system disorders:	
Frequent	Dizziness [4,16,] somnolence [2,16,] headache, extrapyramidal symptoms[1, 21], dysarthria
Less frequent	Seizure[1], restless legs syndrome, tardive dyskinesia[1,5], syncope [4, 16]
Cardiac disorders:	
Frequent	Tachycardia[4], palpitations [23]
Less frequent	QT prolongation[1,12,18], bradycardia[32]
Frequency unknown	Cardiomyopathy, myocarditis
Eye disorders:	
Frequent	Blurred vision
Vascular disorders:	
Frequent	Orthostatic hypotension [4, 16]
Less frequent	Venous thrombo-embolism[1]
Frequency unknown	Stroke [33]
Respiratory, thoracic and mediastinal disorder:	
Frequent	Dyspnoea [23]
Less frequent	Rhinitis

Gastrointestinal disorders:	
Frequent	Dry mouth, constipation, dyspepsia, vomiting[25]
Less frequent	Dysphagia[7], pancreatitis[1], intestinal obstruction/ ileus
Hepato-biliary disorders:	
Frequent	Elevations in serum alanine aminotransferase (ALT)[3], elevations in gamma-GT levels[3]
Less frequent	Elevations in serum aspartate aminotransferase (AST)[3], jaundice[5], hepatitis
Skin and subcutaneous tissue disorders:	
Less frequent	Angioedema[5], Stevens-Johnson syndrome[5]
Frequency unknown	Toxic Epidermal Necrolysis, erythema multiforme, Acute Generalised Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), cutaneous vasculitis
Musculoskeletal and connective tissue disorders:	
Less frequent	Rhabdomyolysis
Renal and urinary disorders:	
Less frequent	Urinary retention
Pregnancy, puerperium and perinatal conditions:	
Frequency unknown	Drug withdrawal syndrome neonatal[31]
Reproductive system and breast disorders:	
Less frequent	Sexual dysfunction, priapism, galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions	
Frequent	Withdrawal (discontinuation) symptoms[1,9], mild asthenia, peripheral oedema, irritability, pyrexia
Less frequent	Neuroleptic malignant syndrome[1], hypothermia

Investigations:	
Less frequent	Elevations in blood creatine phosphokinase[14]

([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 TEVA.

([3]) 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.

([4]) QUETIAPINE TEVA may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see **section 4.4**), because of $alpha_1$ adrenergic blocking activity.

([5]) Calculation of frequency for these ADR's have only been taken from post-marketing data with the immediate release formulation of quetiapine.

([6]) 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.

([7]) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.

([8]) Based on > 7 % increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

([9]) 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.

[10]) 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.

([11]) 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. 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).

([12]) See text below.

([13]) Platelets ≤ 100 x 10^9/L on at least one occasion.

([14]) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

([15]) 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.

([16]) May lead to falls.

([17]) HDL cholesterol: <40 mg/dL (1,025 mmol/L) males; < 50 mg/dL (1,282 mmol/L) females at any time.

([18]) 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.

([19]) Shift from > 132 mmol/L to ≤ 132 mmol/L on at least one occasion.

([20]) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see **sections 4.4** and **5.1**).

([21]) See **section 5.1**.

([22]) 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. For these patients, the mean maximum decrease in haemoglobin at any time was -1,50 g/dL.

([23]) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disease.

([24]) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as < 0,8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.

([25]) Based upon the increased rate of vomiting in elderly patients (≥ 65 years of age).

([26]) Based on shift in neutrophils from >=1,5 x 10^9/L at baseline to <0,5 x 10^9/L at any time during treatment and based on patients with severe neutropenia (<0,5 x 10^9/L) and infection during all quetiapine clinical trials (See **section 4.4**).

([27]) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in eosinophils are defined as ≥1 x 10^9 cells/L at any time.

([28]) Based on shifts from normal baseline to potentially clinically important value at anytime post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x 10^9 cells/L at any time.

([29]) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.

([30]) In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see **section 4.4**).

([31]) See **section 4.6**.

([32]) 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.

([33]) Based on one retrospective non-randomised epidemiological study.

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

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with QUETIAPINE TEVA treatment.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

Symptoms:

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

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death.

In case of overdose with prolonged-release quetiapine (e.g. QUETIAPINE TEVA there is a delayed peak sedation and peak pulse and prolonged recovery compared with immediate-release quetiapine overdose.

Management of overdose:

There is no specific antidote to QUETIAPINE TEVA. 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.

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

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines. ATC code: N05A H04

A2.6.5 Central nervous system depressants: Miscellaneous structures.

Mechanism of action:

Quetiapine is an atypical antipsychotic medicine. 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 D_2- receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic α1- receptors and moderate affinity at adrenergic α2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic effects). Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine prolonged release's therapeutic efficacy as an antidepressant.

Pharmacodynamic effects:

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2-receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine 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 mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration. (See **section 4.8**)

5.2 Pharmacokinetic properties:

Absorption:

Quetiapine is well absorbed following oral administration. Quetiapine achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (T_{max}). Steady-state peak molar concentrations of the active metabolite norquetiapine are 35 % of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When quetiapine prolonged release administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13 % lower at steady state. When quetiapine prolonged release is compared to quetiapine immediate release, the norquetiapine metabolite AUC is 18 % lower.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the quetiapine C_{max}, and AUC of 44 to 52 % and 20 to22 %, respectively, for the 50 mg and 300 mg tablets. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. This increase in exposure is not clinically significant and therefore QUETIAPINE TEVA can be taken with or without food.

Distribution:

Quetiapine is approximately 83 % bound to plasma proteins.

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.

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 medicine. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination:

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73 % of a radiolabelled drug was excreted in the urine and 21 % in the faeces with less than 5 % of the total radioactivity representing unchanged medicine-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5 % excreted in the urine.

Special populations:

Gender:

The pharmacokinetics of quetiapine does not differ between men and women.

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:

The mean plasma clearance of quetiapine was reduced by approximately 25 % in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73 m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment:

The mean quetiapine plasma clearance decreases with approximately 25 % in persons with known hepatic impairment (stable alcohol cirrhosis). 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 **section 4.2**).

Paediatric population:

It has been reported that pharmacokinetic data sampled from children and adolescents who were on steady-state treatment with 400 mg quetiapine twice daily, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10 to 17 years of age) were in general similar to adults, though C_{max} in children was at the higher end of the range observed in adults. The AUC and C_{max} for the active metabolite, norquetiapine, were higher, approximately 62 % and 49 % in children (10 to 12 years), respectively and 28 % and 14 % in adolescents (13 to 17 years), respectively, compared to adults.

No information is available for quetiapine prolonged release in children and adolescents.

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 (for cataracts/lens opacities, see **section 5.1**).

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:

Tablet core

Cellulose, microcrystalline

Hypromellose (Methocel E5 Premium)

Hypromellose (Methocel K100 Premium LV)

Hypromellose (Methocel K4M Premium CR)

Magnesium stearate

Sodium citrate, anhydrous

Tablet coating:

QUETIAPINE 50 TEVA*:* Opadry 15B265003 Brown consisting of HPMC 2910/ hypromellose 3cP, HPMC 2910/ hypromellose 6 cP, iron oxide yellow, iron oxide red, iron oxide black, macrogol/PEG 400, polysorbate 80, titanium dioxide.

QUETIAPINE 200 TEVA: Opadry 15B220002 Yellow consisting of HPMC 2910/ hypromellose 3cP, HPMC 2910/ hypromellose 15 cP, iron oxide yellow, iron oxide red, macrogol/PEG 400, polysorbate 80, titanium dioxide.

QUETIAPINE 300 TEVA: Opadry 15B220003 Yellow consisting of HPMC 2910/ hypromellose 3cP, HPMC 2910/ hypromellose 6 cP, iron oxide yellow, iron oxide red, iron oxide black, macrogol/PEG 400, polysorbate 80, titanium dioxide.

QUETIAPINE 400 TEVA: Opadry YS-1-7003 White consisting of HPMC 2910/ hypromellose 3cP, HPMC 2910/ hypromellose 6 cP, macrogol/PEG 400, polysorbate 80 titanium dioxide.

6.2 Incompatibilities:

Not applicable.

6.3 Shelf life:

3 years.

6.4 Special precautions for storage:

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.

Store at or below 25 °C.

Keep in original packaging till needed for use.

Protect from moisture.

6.5 Nature and contents of container:

QUETIAPINE TEVA film-coated tablets are packed into PVC/Aclar aluminium and PVC/PVDC foil white blisters containing 10, 20, 30, 50, 60, 90 or 100 tablets. Not all pack sizes may be marketed.

White opaque HDPE tablet container with white opaque PP cap integrated with 2 g silica gel desiccant containing 60 tablets.

6.6 Special precautions for disposal and other handling:

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City

Midrand

Gauteng

South Africa

2090

8. REGISTRATION NUMBER(S):

QUETIAPINE 50 TEVA: 47/2.6.5/0657

QUETIAPINE 200 TEVA: 47/2.6.5/0658

QUETIAPINE 300 TEVA: 47/2.6.5/0659

QUETIAPINE 400 TEVA: 47/2.6.5/0660

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

11 August 2020

10. DATE OF REVISION OF THE TEXT:

04 June 2024