Professional information for QUETIAPINE BIOTECH 25, 100, 200, 300

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

QUETIAPINE BIOTECH 25, film-coated tablets

QUETIAPINE BIOTECH 100, film-coated tablets

QUETIAPINE BIOTECH 200, film-coated tablets

QUETIAPINE BIOTECH 300, film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

QUETIAPINE BIOTECH 25:

Each film-coated tablet contains 25 mg of quetiapine free base.

QUETIAPINE BIOTECH 100:

Each film-coated tablet contains 100 mg of quetiapine free base.

QUETIAPINE BIOTECH 200:

Each film-coated tablet contains 200 mg of quetiapine free base.

QUETIAPINE BIOTECH 300:

Each film-coated tablet contains 300 mg of quetiapine free base.

Excipients with known effects:

Contains sugar (QUETIAPINE BIOTECH 25 contains 15,371 mg, QUETIAPINE BIOTECH 100 contains 61,484 mg, QUETIAPINE BIOTECH 200 contains 122,968 mg and QUETIAPINE BIOTECH 300 contains 184,452 mg lactose monohydrate per film-coated tablet).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

QUETIAPINE BIOTECH 25: Round biconvex pink film-coated tablet.

QUETIAPINE BIOTECH 100: Round biconvex yellow film-coated tablet, scored on one side.

QUETIAPINE BIOTECH 200: Round biconvex white film-coated tablet, scored on one side.

QUETIAPINE BIOTECH 300: Oblong biconvex white film-coated tablet, scored on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

QUETIAPINE BIOTECH is indicated for the treatment of schizophrenia.

QUETIAPINE BIOTECH is also indicated for the treatment of manic episodes associated with a bipolar disorder. Safety and efficacy beyond 12 weeks has not been demonstrated.

4.2 Posology and method of administration

Posology

QUETIAPINE BIOTECH should be administered twice daily, with or without food.

Treatment of schizophrenia in adults:

For the treatment of schizophrenia the total daily dose for the first 4 days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). From Day 4 onwards, the dose should be titrated to the effective dose range of 300 – 450 mg/day. However, this may be adjusted, depending on the clinical response and tolerability of the individual patient, within the range 150 – 750 mg/day.

Treatment of manic episodes associated with bipolar disorder in adults:

For the treatment of manic episodes associated with bipolar disorder, the total daily dose for the first 4 days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater

than 200 mg/day.

The dose may be adjusted depending on the clinical response and tolerability of the individual patient, within the range of

200 – 800 mg/day. The usual effective dose is in the range of

400 – 800 mg/day.

Elderly patients:

QUETIAPINE BIOTECH should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on QUETIAPINE BIOTECH 25 mg/day. The dose should be increased daily, in increments of 25 – 50 mg, to an effective dose, depending on the clinical response and the tolerance of the individual patient.

Renal and hepatic impairment:

Clearance of quetiapine is reduced by approximately 25 % in patients with renal or hepatic impairment. Quetiapine is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment. Patients with renal or hepatic impairment should be started on QUETIAPINE BIOTECH 25 mg/day. The dose should be increased daily in increments of 25 – 50 mg, to an effective dose.

Method of administration

Oral administration.

4.3 Contraindications

- QUETIAPINE BIOTECH is contraindicated in patients who are hypersensitive to quetiapine or any of the excipients listed in section 6.1.
- QUETIAPINE BIOTECH should not be used in patients with advanced liver and renal function impairment.
- Pregnancy and lactation, as safety has not been demonstrated.

- Safety and efficacy in children and adolescents under the age of 18 years have not been demonstrated.
- QUETIAPINE BIOTECH is not indicated for use in elderly patients with dementia-related psychosis.
- Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated.

4.4 Special warnings and precautions for use

Paediatric population:

QUETIAPINE BIOTECH 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. 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, elevation 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 (increase 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 BIOTECH on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

QUETIAPINE BIOTECH is associated with an increased incidence of extrapyramidal symptoms (EPS) in children and adolescents.

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

Other psychiatric conditions for which QUETIAPINE BIOTECH 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 be carefully monitored during treatment.

Metabolic risk:

Given the observed risk for worsening of the metabolic profile, including changes in body mass, blood glucose (see hyperglycaemia) and lipids, patients' metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled during treatment. Worsening in these parameters should be managed as clinically appropriate (see section 4.8).

Extrapyramidal symptoms:

QUETIAPINE BIOTECH is associated with an increased incidence of extrapyramidal symptoms (EPS) in patients treated for major depressive episodes in bipolar disorder (see sections 4.8 and 5.1).

The use of QUETIAPINE BIOTECH has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness, and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be

detrimental.

Hyperglycaemia and diabetes mellitus:

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with QUETIAPINE BIOTECH.

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

Where the use of QUETIAPINE BIOTECH in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, over-sedation and complications associated with hyperglycaemia. Before prescribing QUETIAPINE BIOTECH, clinicians are advised to carefully assess the risks and benefits of the use of QUETIAPINE BIOTECH in elderly patients with dementia. In these cases, the risk prediction for stroke in the individual patient (e.g. hypertension, diabetes, current smoking, atrial fibrillation and age > 80 years) must be taken into account.

Elderly patients with dementia-related psychosis:

QUETIAPINE BIOTECH is not approved for the treatment of patients with dementia-related psychosis (see section 4.3).

With some atypical antipsychotics, an approximately 3-fold increased risk of cerebrovascular

adverse events has been seen in the dementia population. The mechanism for this increased risk is not known. QUETIAPINE BIOTECH should be used with caution in patients with risk factors for stroke.

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

Caution should be exercised if QUETIAPINE BIOTECH is prescribed to elderly patients with Parkinson's disease.

Somnolence and dizziness:

QUETIAPINE BIOTECH treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). In patients treated for bipolar depression, 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.

Body mass:

Increase in body mass has been reported in patients who have been treated with QUETIAPINE BIOTECH, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see sections 4.8).

Orthostatic hypotension:

QUETIAPINE BIOTECH 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 QUETIAPINE BIOTECH.

QUETIAPINE BIOTECH 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.

Seizures:

Caution is recommended when treating patients with a history of seizures.

Dysphagia:

Dysphagia and aspiration have been reported with quetiapine as in QUETIAPINE BIOTECH. Although a causal relationship with aspiration pneumonia has not been established, QUETIAPINE BIOTECH should be used with caution in patients at risk for aspiration pneumonia. In patients with Alzheimer's dementia dysphagia associated with use of antipsychotic medications may increase risk of aspiration pneumonia.

QT prolongation:

QT prolongation was reported with quetiapine, as in QUETIAPINE BIOTECH at the therapeutic doses (see section 4.8) and in overdose (see section 4.9).

Caution should be exercised when QUETIAPINE BIOTECH is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when QUETIAPINE BIOTECH is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in patients with increased risk of QT prolongation, i.e. 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. A causal relationship to quetiapine, as in QUETIAPINE BIOTECH, has not been established. Treatment with QUETIAPINE BIOTECH

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) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported with QUETIAPINE BIOTECH treatment. SCARs commonly present as a combination of the following symptoms: extensive cutaneous rash or exfoliative dermatitis, fever, lymphadenopathy, and possible eosinophilia. If signs and symptoms suggestive of these severe skin reactions appear, QUETIAPINE BIOTECH should be withdrawn immediately, and alternative treatment should be considered.

Tardive dyskinesia:

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

The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8).

Sleep apnoea syndrome:

Sleep apnoea syndrome has been reported in patients using QUETIAPINE BIOTECH. 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 BIOTECH should be used with caution.

Severe neutropenia and agranulocytosis:

Severe neutropenia (neutrophil count < 0,5 x 10^9/L) has been reported. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with QUETIAPINE BIOTECH. There was no apparent dose relationship. Resolution of leucopenia and/or neutropenia may follow cessation of therapy with QUETIAPINE BIOTECH. Although a causal

relationship could not be established, the possibility that QUETIAPINE BIOTECH may be implicated cannot be excluded. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of medicine-induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. QUETIAPINE BIOTECH 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).
Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s) and should be managed as clinically appropriate.
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 treatment with QUETIAPINE BIOTECH. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Anticholinergic (muscarinic) effects:

Norquetiapine, an active metabolite of quetiapine, the active ingredient in QUETIAPINE BIOTECH, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to adverse drug reactions (ADRs) reflecting anticholinergic effects when QUETIAPINE BIOTECH is used at recommended doses, when used concomitantly with other medicines having anticholinergic effects, and in the setting of overdose.
QUETIAPINE BIOTECH should be used with caution in patients receiving medicines having anticholinergic (muscarinic) effects. QUETIAPINE BIOTECH should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see sections 4.5, 4.8 and 4.9).

Interactions:

See section 4.5.

Concomitant use of QUETIAPINE BIOTECH with a strong hepatic enzyme inducer such as

carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine, as in QUETIAPINE BIOTECH, therapy.
It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Lipids:

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed with quetiapine, as in QUETIAPINE BIOTECH (see section 4.8). Lipid changes should be managed as clinically appropriate.

Acute withdrawal reactions:

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability may occur after abrupt cessation of QUETIAPINE BIOTECH. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable.

Hepatic effects:

If jaundice develops, QUETIAPINE BIOTECH should be discontinued.

Constipation and intestinal obstruction:

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine, as in QUETIAPINE BIOTECH (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medicines that decrease intestinal motility and/or may not report symptoms of constipation. 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. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with QUETIAPINE BIOTECH and preventative measures undertaken.

Pancreatitis:

Pancreatitis has been reported.

Neuroleptic malignant syndrome:

Neuroleptic malignant syndrome has been associated with QUETIAPINE BIOTECH treatment. Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability and increased creatine phosphokinase. In such an event, QUETIAPINE BIOTECH should be discontinued and appropriate medical treatment given.

Misuse and abuse:

Cases of misuse and abuse have been reported.

Patients with a history of substance or alcohol abuse should be observed closely for signs of misuse or abuse of QUETIAPINE BIOTECH.

Additional information:

Data of quetiapine, as in QUETIAPINE BIOTECH, in combination with lithium in acute moderate to severe manic episodes is limited. Combination therapy was well tolerated (see section 4.8). The data showed an additive effect at week 3.

Lactose monohydrate:

QUETIAPINE BIOTECH tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption

should not take QUETIAPINE BIOTECH.

4.5 Interaction with other medicines and other forms of interaction

QUETIAPINE BIOTECH should be used with caution in combination with other centrally-acting medicines and alcohol.

The central effects of other CNS depressants, including alcohol, may be enhanced by QUETIAPINE BIOTECH.

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

Caution should be taken when co-administering QUETIAPINE BIOTECH with carbamazepine (a known hepatic enzyme inducer) as it can cause increases in clearance of QUETIAPINE BIOTECH.

As a consequence of this interaction lower plasma concentrations can occur, and hence in each patient consideration for a higher dose of QUETIAPINE BIOTECH, depending on clinical response, should be given. The recommended maximum daily dose for the applicable indication should be noted (see section 4.2).

The pharmacokinetics of lithium was not altered when co-administered with QUETIAPINE BIOTECH. Concomitant use of lithium and QUETIAPINE BIOTECH may cause a higher incidence of extrapyramidal related events (tremor), somnolence, and gain in body mass.

The pharmacokinetics of sodium valproate and QUETIAPINE BIOTECH were not altered to a clinically relevant extent when co-administered. Concomitant use of sodium valproate and QUETIAPINE BIOTECH may cause a higher incidence of leucopenia and neutropenia.

The pharmacokinetics of QUETIAPINE BIOTECH were not significantly altered by co-administration of the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

The pharmacokinetics of QUETIAPINE BIOTECH was not significantly altered after co-administration with antipsychotics such as risperidone or haloperidol. However, co-administration of QUETIAPINE BIOTECH and thioridazine caused an increase in clearance of QUETIAPINE

BIOTECH.

QUETIAPINE BIOTECH should be used with caution in patients receiving antihypertensives or medicines that prolong the QT interval (see section 4.4).

QUETIAPINE BIOTECH may antagonise the actions of dopaminergics, such as levodopa.

Co-administration of QUETIAPINE BIOTECH with another microsomal enzyme inducer, phenytoin, can also cause increases in clearance of QUETIAPINE BIOTECH. Increased doses of QUETIAPINE BIOTECH may be required to maintain control of psychotic symptoms in patients co-administered QUETIAPINE BIOTECH and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of QUETIAPINE BIOTECH may need to be reduced if phenytoin, carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

The co-administration of ketoconazole and QUETIAPINE BIOTECH may result in a significant (5-fold) increase in the AUC of QUETIAPINE BIOTECH. For this reason concomitant use of QUETIAPINE BIOTECH and potent CYP3A4 inhibitors is contraindicated (see section 4.3).

It is also not recommended to consume grapefruit juice while on QUETIAPINE BIOTECH treatment.

Clearance of QUETIAPINE BIOTECH was decreased by 20 % when co-administered with cimetidine 400 mg per day.

Mean clearance of lorazepam was decreased by 20 % when co-administered with QUETIAPINE BIOTECH 250 mg three times a day.

4.6 Fertility, pregnancy and lactation

As safety has not been demonstrated, QUETIAPINE BIOTECH is contraindicated during pregnancy and lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

QUETIAPINE BIOTECH may cause dizziness and somnolence which may interfere with activities

requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) with QUETIAPINE BIOTECH are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, increased body mass, decreased haemoglobin and extrapyramidal symptoms.

Adverse reactions arranged by system organ class are as follows:

Blood and lymphatic system disorder

Frequent: Leucopenia (see section 4.4), decreased haemoglobin, decreased neutrophil count, increased eosinophils.

Less frequent: neutropenia (see section 4.4), thrombocytopenia, anaemia, decreased platelet count, agranulocytosis.

Immune system disorders

Less frequent: Hypersensitivity (angioedema, anaphylaxis, urticaria/rash), anaphylactic reactions.

Endocrine disorders

Frequent: Hyperprolactinaemia, decreases in total T4, decreases in free T4, decreases in total T3, increases in TSH.

Less frequent: Inappropriate antidiuretic hormone secretion, hypothyroidism, decreases in free T3.

Metabolism and nutrition disorders

Frequent: Increased appetite, elevations in serum triglyceride levels, elevations in total

cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, body mass gain, increased blood glucose to hyperglycaemic levels.

Less frequent: Diabetes mellitus (or exacerbation of pre-existing diabetes), hyponatraemia, metabolic syndrome.

Psychiatric disorders

Frequent: Abnormal dreams, nightmares, suicidal ideation and suicidal behaviour.

Less frequent: Somnambulism and other related events such as sleep talking and sleep-related eating disorder.

Nervous system disorders

Frequent: Dizziness (see section 4.4), somnolence (see section 4.4), headache, syncope (see section 4.4), dysarthria, anxiety, extrapyramidal symptoms (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity and tremor).

Less frequent: Seizure (see section 4.4), restless leg syndrome, tardive dyskinesia, neuroleptic malignant syndrome.

Eye disorders

Frequent: Dry eyes, blurred vision.

Frequency unknown: Cataract formation.

Ear and labyrinth disorders

Frequency unknown: Ear pain.

Cardiac disorders

Frequent: Tachycardia; palpitations.

Less frequent: Prolongation of QT interval (see section 4.4).

Frequency unknown: Ventricular dysrhythmia; sudden unexplained death, cardiac arrest and

torsades de pointes (as class effects of neuroleptics), bradycardia.

Vascular disorders

Frequent: Orthostatic hypotension (see section 4.4).

Less frequent: Venous thromboembolism.

Frequency unknown: Stroke.

Respiratory, thoracic, and mediastinal disorders

Frequent: Rhinitis, dyspnoea.

Frequency unknown: Chest pain.

Gastrointestinal disorders

Frequent: Dry mouth, constipation, dyspepsia; vomiting.

Less frequent: Abdominal pain, dysphagia, decreased appetite, pancreatitis, intestinal obstruction/Ileus.

Hepato-biliary disorders

Frequent: Elevations in serum alanine aminotransferase (ALT), elevations in gamma-GT levels.

Less frequent: Jaundice; hepatitis, elevations in serum aspartate aminotransferase (AST).

Skin and subcutaneous tissue disorder

Less frequent: Angioedema, Stevens-Johnson syndrome.

Frequency unknown: Toxic epidermal necrolysis, erythema multiforme, drug rash with eosinophilia and systemic symptoms (DRESS).

Musculoskeletal and connective tissue disorders

Less frequent: Back pain, rhabdomyolysis.

Renal and urinary disorders

Less frequent: Urinary retention.

Frequency unknown: Urinary tract infection.

Reproductive system and breast disorders

Less frequent: Sexual dysfunction, priapism, galactorrhoea, breast swelling, menstrual disorder.

General disorders and administration site conditions

Frequent: Asthenia, peripheral oedema, withdrawal (discontinuation) symptoms, pyrexia, irritability.

Less frequent: Myalgia, hypothermia.

Investigations

Less frequent: Elevations in blood creatine phosphokinase.

QUETIAPINE BIOTECH was associated with dose-related decreases in thyroid hormone levels, particularly total T4 and free T4. The reduction in total T4 and free T4 was maximally within the first two to four weeks of QUETIAPINE BIOTECH treatment with no further reduction during long-term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of QUETIAPINE BIOTECH treatment has been associated with reversal of the effects on total and free T4, irrespective of the duration of treatment. Smaller decreases in total and reverse T3 were seen only at higher doses. Levels of TBG were unchanged and, in general, reciprocal increases in TSH were not observed, with any indication that QUETIAPINE BIOTECH causes clinically relevant hypothyroidism.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of QUETIAPINE BIOTECH is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care

providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the “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 quetiapine’s, as in QUETIAPINE BIOTECH, known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anticholinergic effects. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose.

Overdose could lead to QT prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease
may be at an increased risk of the effects of overdose (see section 4.4, Orthostatic hypotension).

Management of overdose

There is no specific antidote to QUETIAPINE BIOTECH. Treatment is symptomatic and supportive. In cases of severe signs, the possibility of multiple medicine involvement should be considered, and an intensive care procedure are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Whilst the prevention of absorption in overdose has not been investigated, the administration of activated charcoal should be considered.

In cases of QUETIAPINE BIOTECH overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Adrenaline

(epinephrine) and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6.5 Tranquillisers, Miscellaneous structures.

Pharmacotherapeutic groups: Antipsychotics; Diazepines, oxazepines and thiazepines

ATC code: N05A H04.

Quetiapine is a dibenzothiazepine atypical antipsychotic agent which interacts with a broad range of neurotransmitter receptors. It is reported to have a higher affinity for serotonin (5HT2) receptors in the brain than it does for dopamine D1 and D2 receptors in the brain. Quetiapine has a high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic, alpha-2 receptors, but no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors. Quetiapine, when given twice a day, maintains 5HT2 and D2 receptor occupancy for up to 12 hours after dosing.

5.2 Pharmacokinetic properties

Absorption:

Quetiapine is well absorbed and extensively metabolised following oral administration, and widely distributed throughout the body. Peak plasma concentrations are reached in about 1,5 hours.

The bioavailability of quetiapine is not significantly affected by administration with food.

Steady-state peak molar concentrations of the active metabolite norquetiapine are 35 % of that observed for quetiapine.

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

Distribution:

It is about 83 % bound to plasma proteins.

Biotransformation:

Quetiapine is extensively metabolised in the liver by sulphoxidation mediated mainly by the cytochrome P450 isoenzyme CYP3A4 and by oxidation.

It is excreted mainly as inactive metabolite with about 73 % of a dose appearing in the urine and about 20 % in the faeces.

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 medicines will result in clinically significant medicine inhibition of cytochrome P450- mediated metabolism of the other medicine.

Elimination:

The elimination half-lives of quetiapine and norquetiapine have been reported to be approximately 7 and 12 hours, respectively.

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 are variable but do not differ significantly between men and women.

Elderly patients

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 subjects with known hepatic impairment (stable alcoholic 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).

5.3 Preclinical safety data

No data of therapeutic relevance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Colloidal anhydrous silica

Glycerol dibehanate

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone K-25

Sodium starch glycolate (type A)

Coating:

Lactose monohydrate

Hypromellose

Macrogol 4000

Red iron oxide (colourant for 25 mg strength)

Titanium dioxide

Yellow iron oxide (colourant for 100 mg strength).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Keep the blister strips in the outer carton until required for use.

6.5 Nature and contents of container

30; 60; 90 or 100 tablets are packed in polyamide/aluminium/PVC blister strips or PVC/aluminium and aluminium blister strips. Each contains ten tablets. The blister strips are packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd

Ground Floor, Block K West, Central Park

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8. REGISTRATION NUMBERS

QUETIAPINE BIOTECH 25: 45/2.6.5/0212

QUETIAPINE BIOTECH 100: 45/2.6.5/0213

QUETIAPINE BIOTECH 200: 45/2.6.5/0214

QUETIAPINE BIOTECH 300: 45/2.6.5/0215

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 31 July 2014

10. DATE OF REVISION OF THE TEXT

10 July 2021