SCHEDULING STATUS: S5

1 NAME OF THE MEDICINE

TRUVALIN® 25; TRUVALIN® 100; TRUVALIN® 200; TRUVALIN® 300 Film-coated Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

TRUVALIN 25:

Each tablet contains quetiapine fumarate equivalent to 25 mg of quetiapine free base.

TRUVALIN 100:

Each tablet contains quetiapine fumarate equivalent to 100 mg of quetiapine free base.

TRUVALIN 200:

Each tablet contains quetiapine fumarate equivalent to 200 mg of quetiapine free base.

TRUVALIN 300*:*

Each tablet contains quetiapine fumarate equivalent to 300 mg of quetiapine free base.

Contains sugar: lactose monohydrate 19 mg (25 mg tablet); 20,70 mg (100 mg tablet); 41,40 mg (200 mg tablet); 62,10 mg (300 mg tablet).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated Tablet

TRUVALIN 25:

Peach, round, bi-convex, film-coated tablet intagliated with Q 25.

TRUVALIN 100:

Yellow, round, bi-convex, film-coated tablet intagliated with Q 100.

TRUVALIN 200:

White, round, bi-convex, film-coated tablet intagliated with Q 200.

TRUVALIN 300:

White, capsule-shaped, film-coated tablet intagliated with Q on one side and 300 on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TRUVALIN is indicated for the treatment of schizophrenia.

TRUVALIN 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

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

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. Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted in some patients within the range 150-750 mg/day.

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.

Special Populations

Elderly:

TRUVALIN should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on TRUVALIN 25 mg/day. The dose should be increased daily, in increments of 25-50 mg, to an effective dose, which is likely to be lower than that in younger patients.

Renal and hepatic impairment:

The clearance of TRUVALIN is reduced by approximately 25 % in patients with renal or hepatic impairment. TRUVALIN is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment.

4.3 Contraindications

- TRUVALIN is contra-indicated in patients who are hypersensitive to any component of this product.
- Pregnancy and lactation, as safety has not been demonstrated.
- Safety and efficacy in children and adolescents have not been demonstrated.
- Advanced liver and renal function impairment, as safety has not been demonstrated.

4.4 Special warnings and precautions for use

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.

Other psychiatric conditions for which TRUVALIN is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may co-morbid with major depression disorder. The same precaution observed when treating patients with major depressive disorder should therefore be observed when treating 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.

Neutropenia and agranulocytosis:

Severe neutropenia (<0,5 X 10^9/L) without infection has been uncommonly reported in short-term placebo-controlled monotherapy quetiapine clinical trials. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with TRUVALIN 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.

TRUVALIN should be discontinued in patients with a neutrophil count <1,0 X 10^9/L. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 X 10^9/L) (see section 4.8).

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 TRUVALIN.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics such as TRUVALIN 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 TRUVALIN 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 TRUVALIN should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic such as TRUVALIN was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

Lipids:

Increases in triglycerides and cholesterol and decreases in HDL have been observed with TRUVALIN (see section 4.8). 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. Among the 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 (see section 4.4 Lipids), gallstones and alcohol consumption.

Concomitant illness:

TRUVALIN should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. TRUVALIN may induce orthostatic hypotension, especially during the initial dose-titration period; this is more common in elderly patients than in younger patients.

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

Dysphagia:

Dysphagia (see section 4.8) and aspiration have been reported with TRUVALIN. TRUVALIN 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 TRUVALIN (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.

Seizures:

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

Tardive dyskinesia and Extrapyramidal Symptoms (EPS):

There is a potential for TRUVALIN to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, discontinuation of TRUVALIN 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 TRUVALIN 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 TRUVALIN treated patients than in placebo treated patients (see section 4.8).

Neuroleptic malignant syndrome:

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

QT prolongation:

In clinical trials, TRUVALIN was not associated with a persistent increase in QTc intervals. However, caution should be exercised when TRUVALIN is prescribed with medicines known to prolong the QTc interval, especially in the elderly.

Cardiomyopathy and Myocarditis:

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience. Treatment with TRUVALIN 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) are potentially life-threatening adverse drug reactions that have been reported during TRUVALIN 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 TRUVALIN if severe cutaneous adverse reactions occur.

Withdrawal:

Acute withdrawal symptoms such as insomnia, nausea, and vomiting have been described after abrupt cessation of antipsychotic medicines, including TRUVALIN. Gradual withdrawal over a period of at least 1-2 weeks is advisable.

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.

Elderly patients with dementia:

Before prescribing, medical practitioners are advised to carefully assess the risks and benefits of the use of atypical antipsychotics in elderly patients with dementia.

TRUVALIN is not approved for the treatment of dementia-related psychosis. In a meta-analysis of atypical antipsychotic medicines, 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: 56-99 years) the incidence of mortality in quetiapine treated patients was 5,5 % versus 3,2 % in the placebo group.

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 TRUVALIN is used at recommended doses, when used concomitantly with other medications having anticholinergic effects, and in the setting of overdose. TRUVALIN should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. TRUVALIN 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, 5.1, and 4.9).

Lactose:

TRUVALIN contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, or glucose-galactose malabsorption should not take TRUVALIN.

4.5 Interaction with other medicines and other forms of interaction

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

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

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

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

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

The pharmacokinetics of TRUVALIN were not significantly altered following co-administration with the antipsychotics, risperidone or haloperidol. However, co-administration of TRUVALIN and thioridazine caused increases in clearance of TRUVALIN.

TRUVALIN did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. In a multiple dose trial in patients to assess the pharmacokinetics of TRUVALIN given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of TRUVALIN. This increase in clearance reduced systemic TRUVALIN exposure (as measured by AUC) to an average of 13 % of the exposure during administration of TRUVALIN 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 TRUVALIN, depending on clinical response, should be considered. It should be noted that the recommended maximum daily dose of TRUVALIN is 750 mg/day, for the treatment of schizophrenia, and 800 mg/day for the treatment of manic episodes associated with bipolar disorder.

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 TRUVALIN and with another microsomal enzyme inducer, phenytoin, also caused increases in the clearance of TRUVALIN. Increased doses of TRUVALIN may be required to maintain control of psychotic symptoms in patients co-administered TRUVALIN and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc). The dose of TRUVALIN 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).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of TRUVALIN. The pharmacokinetics of TRUVALIN were not altered following co-administration with cimetidine or fluoxetine, both of which are known P450 enzyme inhibitors. The pharmacokinetics of TRUVALIN were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor). In a multiple-dose trial in healthy volunteers to assess the pharmacokinetics of TRUVALIN given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean C_{max} and AUC of TRUVALIN of 235 % and 522 %, respectively, with a corresponding decrease in mean oral clearance of 84 %. The mean half-life of TRUVALIN increased from 2,6-6,8 hours, but the mean t_{max} was unchanged. Due to the potential for an interaction of similar magnitude in a clinical setting, the dosage of TRUVALIN should be reduced during concomitant use of TRUVALIN and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

TRUVALIN is contraindicated during pregnancy and lactation, as safety has not been demonstrated.

Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported.

Breastfeeding

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent.

4.7 Effects on ability to drive and use machines

TRUVALIN may cause 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

a. Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) with TRUVALIN (≥ 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.

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Event
Blood and lymphatic system disorders	Common (≥ 1 % - < 10 %)	Leukopenia [a, x]
	Very rare (< 0,01%)	Neutropenia [ab]
Immune system disorders	Uncommon (≥ 0,1 % - < 1 %)	Hypersensitivity [f]
Metabolism and nutrition disorders	Common (≥ 1 % - < 10 %)	Increased appetite
Psychiatric disorders	Common (≥ 1 % - < 10 %)	Abnormal dreams and nightmares
	Rare (≥ 0,01 % - < 0,1 %)	Somnambulism and other related events
Nervous system disorders	Very common (≥ 10 %)	Dizziness [a, e, q] Somnolence [b, q] Extrapyramidal symptoms [a, p]

	Common (≥ 1 % - < 10 %)	Dysarthria Anxiety
	Uncommon (≥ 0,1 % - < 1 %)	Seizure [a] Syncope [a, e, q] Restless legs syndrome Tardive dyskinesia [a] Confusional state
Eye disorders	Common (≥ 1 % - < 10 %)	Vision blurred [s]
Cardiac disorders	Common (≥ 1 % - < 10%)	Tachycardia [a, e] Palpitations [t]
	Uncommon (≥ 0,1 % - < 1 %)	Bradycardia [y]
Vascular disorders	Common (≥ 1 % - < 10 %)	Orthostatic hypotension [a, e, q]
Respiratory, thoracic, and mediastinal disorders	Common (≥ 1 % - < 10 %)	Dyspnoea [t]
	Uncommon (≥ 0,1 % - < 1%)	Rhinitis
Gastrointestinal disorders	Very common (≥ 10 %)	Dry mouth
	Common (≥ 1 % - < 10 %)	Constipation Dyspepsia Vomiting [v]
	Uncommon (≥ 0,1 % - < 1 %)	Dysphagia[a,i]
	Rare (≥ 0,01 % - < 0,1 %)	Intestinal obstruction/Ileus
Hepatobiliary disorders	Rare (≥ 0,01 % - < 0,1 %)	Hepatitis (with or without jaundice)
Skin and subcutaneous tissue disorders	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS) Acute Generalized Exanthematous Pustulosis (AGEP) Erythema multiforme (EM) Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	Very rare	Rhabdomyolysis
Renal and urinary	Common (≥ 1 % - < 10 %)	Urinary tract infection

disorders	Uncommon (≥ 0,1 % - < 1%)	Urinary retention
Reproductive system and breast disorders	Rare (≥ 0,01 % - < 0,1 %)	Priapism Galactorrhoea
General disorders and administration site conditions	Very common (≥ 10 %)	Headache Withdrawal (discontinuation) symptoms [a, j]
	Common (≥ 1 % - < 10 %)	Asthenia Peripheral oedema Irritability Pyrexia
	Rare (≥ 0,01 % - < 0,1 %)	Neuroleptic malignant syndrome [a] Hypothermia
	Not known	Neonatal withdrawal [aa]
Investigations	Very common (≥ 10 %)	Elevations in serum triglyceride levels [a,k] Elevations in total cholesterol [a,l] Decreases in HDL cholesterol [a,r] Weight gain [c] Decreased haemoglobin [s]
	Common (≥ 1 % - < 10 %)	Elevations in serum alanine aminotransferase (ALT) [d] Elevations in gamma-GT levels [d] Neutrophils count decreased [a,g] Eosinophils increased [w] Blood glucose increased to hyperglycaemic level [a,h] Elevations in serum prolactin [o] Decreases in Total T_4 [u] Decreases in Free T_4 [u] Decreases in Total T_3 [u] Increases in TSH [u]
	Uncommon (≥ 0,1 % - < 1 %)	Elevations in serum aspartate

		aminotransferase (AST) [d] Platelet count decreased [n] Decreases in free T_3 [u]
	Rare (≥ 0,01 % - < 0,1 %)	Elevations in blood creatinine phosphokinase [m] Agranulocytosis [z]

[a] See section 4.4 Special warnings and precautions for use

[b] Somnolence may occur, usually during the first 2 weeks of treatment and generally resolves with the continued administration of TRUVALIN.

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

[d] Asymptomatic elevations (shift from normal to ≥ 3X ULN at any time) in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in patients administered TRUVALIN. These elevations were usually reversible on continued TRUVALIN treatment.

[e] TRUVALIN may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period.

[f] Manifestations of hypersensitivity may include angioedema, anaphylaxis and urticaria/rash

[g] In all short-term placebo-controlled monotherapy trials among patients with a baseline neutrophil count ≥ 1,5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <1,5 X10^9/L, was 1,9 % in patients treated with quetiapine compared to1,5 % in placebo-treated patients. The incidence >0,5 - <1,0 x 10^9/L was 0,2 % in patients treated with quetiapine and 0,2 % in placebo-treated patients. In clinical trials conducted prior to a protocol amendment for discontinuation of patients with treatment- emergent neutrophil count <1,0 x 10^9/L, among patients with a baseline neutrophil count ≥1,5 X 10^9/L, the incidence of at least one occurrence of neutrophil count <0,5 X 10^9/L was 0,21 % in patients treated with quetiapine and 0 % in placebo treated patients.

[h] Fasting blood glucose ≥126 mg/dL or a non-fasting blood glucose ≥200 mg/dL on at least one occasion.

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

[j] In acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms, the aggregated incidence of discontinuation symptoms after abrupt cessation was

12,1 % for quetiapine and 6,7 % for placebo. The aggregated incidence of the individual adverse events (e.g., insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability) did not exceed 5,3 % in any treatment group and usually resolved after 1 week post- discontinuation.

[k] Triglycerides ≥ 200 mg/dL (patients ≥ 18 years of age) or ≥ 150 mg/dL (patients <18 years of age) on at least one occasion.

[l] Cholesterol ≥240 mg/dL (patients ≥18 years of age) or ≥ 200 mg/dL (patients <18 years of age) on at least one occasion.

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

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

[o] Prolactin levels (patients ≥18 years of age): > 20 µg/L males; > 30 µg/L females at any time.

[p] See text below in sub-heading "*c. Description of selected adverse reactions"*

[q] May lead to falls.

[r] HDL cholesterol: <40 mg/dL males; <50 mg/dL females at any time.

[s] 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.

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

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

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

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

[x] Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤ 3X10^9 cells/L at any time.

[y] 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.

[z] Based on the frequency of patients during all quetiapine clinical trials with severe neutropenia

(<0.5 x 10^9/L) and infection.

[aa] See section 4.6 Pregnancy and lactation.

[ab] During post-marketing experience, resolution of leucopenia and/or neutropenia usually followed cessation of therapy with TRUVALIN. Possible risk factors for leucopenia and/or neutropenia include pre-existing low white cell count and history of medicine induced leucopenia and/or neutropenia. Other adverse events reported since market introduction, which were temporally related to quetiapine therapy, but not necessarily causally related, include agranulocytosis.

c. Description of selected adverse reactions

TRUVALIN treatment was associated with dose-related decreases in thyroid hormone levels. In short term placebo-controlled clinical trials, the incidence of potentially clinically significant shifts in thyroid hormone levels were total T_4: 3,4 % for quetiapine versus 0,6 % for placebo; free T_4: 0,7 % for quetiapine versus 0,1 % for placebo; total T_3: 0,54 % for quetiapine versus 0,0 % for placebo and free T_3: 0,2 % for quetiapine versus 0,0 % for placebo. The incidence of shifts in TSH was 3,2 % for quetiapine versus 2,7 % for placebo. In short term placebo-controlled monotherapy trials, the incidence of reciprocal, potentially clinically significant shifts in T_3 and TSH was 0,0 % for both quetiapine and placebo and 0,1 % for quetiapine versus 0,0 % for placebo for shifts in T_4 and TSH. These changes in thyroid hormone levels are generally not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of TRUVALIN 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 TRUVALIN treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. In eight patients, where TBG was measured levels of TBG were unchanged.

Extrapyramidal symptoms (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity and tremor) occur at an incidence similar to placebo and are not dose related.

TRUVALIN may cause prolongation of the QTc interval (see section 4.4).

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. Health care 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

In clinical trials, experience with TRUVALIN in overdosage is limited. In post-marketing experience, there have been very rare reports of overdose of TRUVALIN alone resulting in death or coma.

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

Management of overdose

There is no specific antidote to quetiapine. Treatment is symptomatic and supportive. 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).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 2.6.5 Central nervous system depressants: Miscellaneous structures

Quetiapine is an atypical antipsychotic agent, which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin ($5HT_2$) receptors in the brain than it does for dopamine D_1 and D_2 receptors in the brain. 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 $5HT_{1A}$ sites by norquetiapine may contribute to TRUVALIN'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 several

muscarinic receptor subtypes, which may explain anti-cholinergic (muscarinic) effects.

In animal models, quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance

Quetiapine does not produce sustained elevations in prolactin in man.

Quetiapine, when given twice a day, maintains $5HT_2$ and D_2 receptor occupancy for up to 12 hours after dosing.

5.2 Pharmacokinetic properties

Quetiapine is absorbed and extensively metabolised following oral administration. The principal human plasma metabolites do not have significant pharmacological activity. The bioavailability of quetiapine is not significantly affected by administration with food. The elimination half-life of quetiapine is approximately 7 hours. Quetiapine is approximately 65 %-83 % bound to plasma proteins.

The pharmacokinetics of quetiapine are variable but do not differ significantly between men and women.

The mean clearance of quetiapine in the elderly is approximately 30-50 % lower than that seen in adults aged 18-65 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/1,73m^2) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects.

Quetiapine is extensively metabolised with the parent compound accounting for less than 5 % of unchanged medicine-related material in the urine or faeces, following the administration of radio-labelled quetiapine. Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

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

Quetiapine and several of its metabolites were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities, but only at concentrations at least 10-50 fold higher than those observed

in the usual effective dose range of 300-450 mg/day in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Calcium hydrogen phosphate

Microcrystalline cellulose

Sodium starch glycolate

Lactose monohydrate

Magnesium stearate

Povidone

Coating:

Methylhydroxypropylcellulose

Macrogol

Titanium dioxide

Ferric oxide, yellow (25 mg, 100 mg tablets)

Ferric oxide, red (25 mg tablets)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 30 °C.

Protect from moisture.

Do not remove from carton until required for use

6.5 Nature and contents of container

TRUVALIN tablets are packed into white opaque PVC aluminum foil blisters with each blister strip containing 6 or 10 tablets, packed into unit cartons.

TRUVALIN 25: Packs of 6 or 100 tablets.

TRUVALIN 100: Packs of 60, 90 or 100 tablets

TRUVALIN 200: Packs of 60, 90 or 100 tablets

TRUVALIN 300: Packs of 60, 90 or 100 tablets

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

AstraZeneca Pharmaceuticals (Pty) Limited

Building 2 Northdowns Office Park

17 Georgian Crescent West

Bryanston, Johannesburg, 2191

South Africa

8 REGISTRATION NUMBERS

TRUVALIN 25: 43/2.6.2/0159

TRUVALIN 100: 43/2.6.2/0160

TRUVALIN 200: 43/2.6.2/0161

TRUVALIN 300: 43/2.6.2/0162

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 November 2011

10 DATE OF REVISION OF THE TEXT

29 March 2023