SCHEDULING STATUS S5

1. NAME OF THE MEDICINE

TORQUIT 25 25 mg film coated tablets
TORQUIT 100 100 mg film coated tablets
TORQUIT 200 200 mg film coated tablets
TORQUIT 300 300 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TORQUIT 25 contains 25 mg quetiapine (as quetiapine fumarate).
TORQUIT 100 contains 100 mg quetiapine (as quetiapine fumarate).
TORQUIT 200 contains 200 mg quetiapine (as quetiapine fumarate).
TORQUIT 300 contains 300 mg quetiapine (as quetiapine fumarate).

Excipients with known effect:
TORQUIT 25 contains 5,447 mg lactose monohydrate.
TORQUIT 100 contains 21,788 mg lactose monohydrate.
TORQUIT 200 contains 43,576 mg lactose monohydrate.
TORQUIT 300 contains 65,364 mg lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

TORQUIT 25 tablets are brownish red coloured, round, biconvex film coated tablets, plain on both sides.
TORQUIT 100 tablets are white to off-white, round, biconvex film coated tablets and plain on both sides.
TORQUIT 200 tablets are white to off-white, round, biconvex film coated tablets with a break line on one side and plain
on other side.
TORQUIT 300 tablets are white to off-white, capsule shaped, biconvex film coated tablets with break line on both sides.

The **TORQUIT 200** and **TORQUIT 300** tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology
TORQUIT should be administered twice daily, with or without food.

Adults
For the treatment of schizophrenia
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.

For the treatment of manic episodes associated with bipolar disorder
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
As with other psychotics, TORQUIT should be used with caution in the elderly, especially during the initial dosing period. Elderly patients should be started on TORQUIT 25 mg/day. The rate of dose titration may need to be slower, in increments of 25 - 50 mg, depending on the clinical response and tolerability of the individual patient, to an effective dose, which is likely to be lower than that in younger patients.

Renal and hepatic impairment
The oral clearance of TORQUIT is reduced by approximately 25 % in patients with renal or hepatic impairment. TORQUIT 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 TORQUIT 25 mg/day. The dose should be increased daily in increments of 25 - 50 mg, to an effective dose.

Paediatric population
The safety and efficacy of TORQUIT in children and adolescents below 18 years of age have not been established.

Method of administration
Oral administration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy and lactation, as the safety has not been established in this population.
- Children and adolescents, as the safety and efficacy have not been demonstrated in this population.
- Advanced liver and renal function impairment, as safety has not been demonstrated.
- Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin, clarithromycin and nefazodone, is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Suicide/suicidal thoughts or clinical worsening
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, healthcare professionals should consider the potential risk of suicide-related events after abrupt cessation of TORQUIT treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which TORQUIT 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.

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). 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, patients' 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 of TORQUIT to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of TORQUIT should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8).
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.
In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see section 4.8).
The use of quetiapine 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.

Somnolence and dizziness
Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8).
For the treatment of patients with bipolar depression, it was demonstrated that the 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 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 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. 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, TORQUIT should be used with caution.

Seizures
It has been shown that there is no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, 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 (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Severe neutropenia and agranulocytosis
Severe neutropenia (neutrophil count <0,5 x 109/L) without infection has been reported in quetiapine clinical trials. There have been reports of agranulocytosis (severe neutropenia with infection) among all patients treated with quetiapine, as contained in TORQUIT, 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 in patients without pre-existing risk factors. Quetiapine should be considered in patients presenting with infection, particularly in the absence of obvious predisposing factor(s), or in patients with unexplained fever, and should be managed as clinically appropriate. Quetiapine should be discontinued in patients with a neutrophil count <1,0 x 109/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 x 109/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 TORQUIT 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 is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose.
TORQUIT should be used with caution in patients receiving medicines having anti-cholinergic (muscarinic) effects.
TORQUIT 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 section 4.5, section 4.8, section 5.1 and section 4.9).

Interactions
See section 4.5.
Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of TORQUIT therapy. In patients receiving a hepatic enzyme inducer, initiation of TORQUIT treatment should only occur if the medical professional considers that the benefits of quetiapine 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).

Weight
Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see section 4.8 and section 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 quetiapine, as contained in TORQUIT (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines.
Patients with an established diagnosis of diabetes mellitus who are started on TORQUIT 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 TORQUIT should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with quetiapine should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when TORQUIT was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Lipids
Increases in triglycerides, low-density lipoproteins (LDL) and total cholesterol, and decreases in high-density lipoproteins (HDL) cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate.

QT prolongation
In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see section 4.8) and in overdose (see section 4.9). Caution should be exercised when TORQUIT is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when TORQUIT 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 should be reassessed in patients with suspected cardiomyopathy or myocarditis.

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

Elderly patients with dementia-related psychosis
TORQUIT 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 - 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 is prescribed to elderly patients with PD.

Dysphagia
Dysphagia (see section 4.8) has been reported with quetiapine. TORQUIT should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction
Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see 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, including TORQUIT, often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine 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.

Additional information
Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and section 5.1). The data showed an additive effect at week 3.

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

Paediatric population
TORQUIT 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 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).

Lactose
TORQUIT tablets contain lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should talk to their doctor or pharmacist before taking TORQUIT.
The small amount of lactose in each dose is unlikely to cause symptoms in adults with lactose intolerance.

4.5 Interactions with other medicines and other forms of interaction

Given the primary central nervous system effects of quetiapine, TORQUIT should be used with caution in combination with other centrally acting medicinal products 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 with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

Quetiapine 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 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 therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450 %. In patients receiving a hepatic enzyme inducer, initiation of TORQUIT treatment should only occur if the medical professional considers that the benefits of quetiapine 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).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine (as in TORQUIT). The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine (as in TORQUIT) 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 quetiapine (as in TORQUIT) given before and during treatment with ketoconazole, co-administration of ketoconazole resulted in an increase in mean Cmax and AUC of quetiapine (as in TORQUIT) of 235 % and 522 %, respectively, with a corresponding decrease in mean oral clearance of 84 %. The mean half-life of quetiapine (as in TORQUIT) increased from 2,6 to 6,8 hours, but the mean tmax was unchanged.

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

The pharmacokinetics of lithium were not altered when co-administered with quetiapine (as in TORQUIT).

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

Caution should be exercised when TORQUIT is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
TORQUIT is contraindicated for the use during pregnancy, as safety has not been demonstrated (see section 4.3).

Breastfeeding
TORQUIT is contraindicated for the use during lactation, as safety has not been demonstrated (see section 4.3).

Fertility
No data on male and female fertility is available.

4.7 Effects on ability to drive and use machines

TORQUIT may cause somnolence which may interfere with activities requiring mental alertness. Patients should be advised not to drive or operate machinery, until individual susceptibility is known. It is not always possible to predict to what extent TORQUIT may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which TORQUIT affects them.

4.8 Undesirable effects

a. Summary of the safety profile
The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine (≥ 10 %) 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, weight gain, decreased haemoglobin and extrapyramidal symptoms.
Other undesirable effects include dry mouth, asthenia, constipation, tachycardia, orthostatic hypotension and dyspepsia.

Syncope, neuroleptic malignant syndrome, leucopenia, neutropenia and peripheral oedema, have been associated with quetiapine as in TORQUIT.

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Adverse Event
Blood and lymphatic system disorders	Frequent	Decreased neutrophil count, decreased haemoglobin[2], eosinophils increased[27], leucopenia[1, 28].
	Less frequent	Agranulocytosis[26], anaemia, neutropenia[1], platelet count decreased[13], thrombocytopenia.
Immune system disorders	Less frequent	Anaphylactic reaction[5], hypersensitivity (including allergic skin conditions)
Endocrine disorders	Frequent	Hyperprolactinaemia[15], decreases in total T4[24], decreases in free T4[24], decreases in total T3[24], increases in TSH[24].
	Less frequent	Decreases in free T3[24], hypothyroidism[21], inappropriate antidiuretic hormone secretion.
Metabolism and nutrition disorders	Frequent	Blood glucose increased to hyperglycaemic levels[6, 30], decreases in HDL cholesterol[17,30], elevations in serum triglyceride levels[10,30], elevations in total cholesterol (predominantly LDL cholesterol)[11,30], increased appetite, weight gain[8,30].
	Less frequent	Diabetes mellitus[1,5], exacerbation of pre-existing diabetes, hyponatraemia[19], 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], dysarthria, extrapyramidal symptoms[1, 21], headache, somnolence[2,16].
	Less frequent	Restless legs syndrome, seizure[1], syncope[4,16], tardive dyskinesia[1, 5].
Eye disorders	Frequent	Blurred vision.
Cardiac disorders	Frequent	Palpitations[23], tachycardia[4].
	Less frequent	Bradycardia[32], QT prolongation[1,12,18].
Vascular disorders	Frequent	Orthostatic hypotension[4,16].
	Less frequent	Stroke[33], venous thromboembolism1.
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea[23].
	Less frequent	Rhinitis.
Gastrointestinal disorders	Frequent	Constipation, dry mouth, dyspepsia, vomiting[25].
	Less frequent	Dysphagia[7], intestinal obstruction/Ileus pancreatitis[1].
Hepato-biliary disorders	Frequent	Elevations in gamma-GT levels[3], Elevations in serum alanine aminotransferase (ALT)[3].
	Less frequent	Elevations in serum aspartate aminotransferase (AST)[3], hepatitis, jaundice[5].
Skin and subcutaneous tissue disorders	Less frequent	Angioedema[5], medicine rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, Stevens- Johnson syndrome[5], toxic epidermal necrolysis.
Musculoskeletal and connective tissue disorders	Less frequent	Rhabdomyolysis.
Renal and urinary disorders	Less frequent	Urinary retention.
Pregnancy, puerperium and perinatal conditions	Less frequent	Medicine withdrawal syndrome neonatal[31]
Reproductive system and breast disorders	Less frequent	Breast swelling, galactorrhoea, menstrual disorder, priapism, sexual dysfunction.
General disorders and administration site conditions	Frequent	Irritability, mild asthenia, peripheral oedema, pyrexia, withdrawal (discontinuation) symptoms[1,9].
	Less frequent	Neuroleptic malignant syndrome[1], hypothermia.
	Unknown frequency	Neonatal withdrawal.
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.
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. As with other antipsychotics with alpha1 adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see section 4.4).
5. Calculation of frequency for these ADR's has been taken from post-marketing data only.
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 109/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 section 4.4 and section 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 any time post-baseline in all trials.
Shifts in total T4, free T4, total T3 and free T3 are defined as <0,8 x LLN (pmol/L) and shift in TSH is > 5 mIU/L at any time.
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 109/L at baseline to <0,5 x 109/L at any time during treatment and based on patients with severe neutropenia (<0,5 x 109/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 any time post-baseline in all trials. Shifts in eosinophils are defined as >1 x 109 cells/L at any time.
28. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤3 x 109 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 sections 4.3 and 4.6 – TORQUIT is contraindicated in pregnancy.
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 arrhythmia, 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) medicine reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with quetiapine treatment.

c. Description of selected adverse reactions
TORQUIT treatment was associated with dose-related decreases in thyroid hormone levels, particularly total T_4 and free T_4. The reduction in total and free T_4 was maximal within the first 2 to 4 weeks of TORQUIT 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 TORQUIT treatment was associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment. Smaller decreases in total T_3 and reverse T_3 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 (as in TORQUIT) causes clinically relevant hypothyroidism.

The following adverse events seen in clinical trials are not medicine related and their frequencies are unknown: headache, abdominal pain, back pain, chest pain, hypertension, diarrhoea, myalgia, anxiety, dry eyes, ear pain and urinary tract infection.

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.

TORQUIT 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. Healthcare professionals 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 clinical trials, experience with quetiapine (as in TORQUIT) in overdosage is limited. In postmarketing experience, there have been very rare reports of overdose of quetiapine 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 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. 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. In cases of severe signs, the possibility of multiple medicines 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.
Based on public literature, patients with delirium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1 - 2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

The administration of activated charcoal should be considered.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic medicines. Epinephrine (adrenaline) and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.
Close medical supervision and monitoring should be continued until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 2.6.5 Central nervous system depressants: Miscellaneous structures
Pharmacotherapeutic group: Diazepines, oxazepines and thiazepines not yet assigned
ATC code: N05A H04

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 (5HT2) 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 (as in TORQUIT) compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but 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 at several muscarinic receptors, which may explain anticholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine'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 is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D[2] receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D[2] receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the 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 and extensively metabolised following oral administration. 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
Quetiapine is approximately 65 % - 83 % bound to plasma proteins.

Biotransformation
Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged medicine-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.

Approximately 73 % of the radioactivity is excreted in the urine and 21 % 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. 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. 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 kinetics of quetiapine do 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/1,73m²), but the individual clearance values are within the range for normal subjects.

Hepatic impairment
The mean quetiapine plasma clearance decreases with approx. 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).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium hydrogen phosphate dihydrate
Colloidal anhydrous silica
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose
Povidone (K-30)
Sodium starch glycolate (Type-A)

Coating composition:
TORQUIT 25
Ferric oxide Red (E172)
Ferric oxide Yellow (E172)
Hypromellose 2910 (6cps)
Macrogol 400
Titanium Dioxide (E171)

TORQUIT 100
Hypromellose 2910 (6cps)
Macrogol 400
Titanium Dioxide (E171)

TORQUIT 200
Hypromellose 2910 (6cps)
Macrogol 400
Titanium Dioxide (E171)

TORQUIT 300
Hypromellose 2910 (6cps)
Macrogol 400
Titanium Dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.
Store at or below 25 °C.

6.4 Special precautions for storage

No special precautions for storage required.

6.5 Nature and contents of container

Blister pack of white opaque PVC film (0,25mm) sealed with printed aluminium lidding foil (thickness 0.025mm) with heat seal lacquer (PVC/PVAC copolymer and polymethacrylate). Each blister strip contains 10 tablets. The blister strips will be packed in an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused product should be disposed of in accordance with local requirements.
No special requirements.

7. MARKETING AUTHORISATION HOLDER

TRINITY PHARMA (PTY) LTD
106, 16th Road,
Midrand,
1686,
South Africa.

8. MARKETING AUTHORISATION NUMBER(S)

TORQUIT 25: 46/2.6.5/0804
TORQUIT 100: 46/2.6.5/0805
TORQUIT 200: 46/2.6.5/0806
TORQUIT 300: 46/2.6.5/0807

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

31 August 2021

10. DATE OF REVISION OF THE TEXT

N.A

SKEDULERINGSTATUS S5

1. NAAM VAN DIE MEDISYNE

TORQUIT 25 25 mg filmbedekte tablette
TORQUIT 100 100 mg filmbedekte tablette
TORQUIT 200 200 mg filmbedekte tablette
TORQUIT 300 300 mg filmbedekte tablette

2. KWALITATIEWE EN KWANTITATIEWE SAMESTELLING

TORQUIT 25 bevat 25 mg kwetiapien (as kwetiapienfumaraat).
TORQUIT 100 bevat 100 mg kwetiapien (as kwetiapienfumaraat).
TORQUIT 200 bevat 200 mg kwetiapien (as kwetiapienfumaraat).
TORQUIT 300 bevat 300 mg kwetiapien (as kwetiapienfumaraat).

Hulpstowwe met bekende effek:
TORQUIT 25 bevat 5,447 mg laktose monohidraat.
TORQUIT 100 bevat 21,788 mg laktose monohidraat.
TORQUIT 200 bevat 43,576 mg laktose monohidraat.
TORQUIT 300 bevat 65,364 mg laktose monohidraat.

Vir 'n volledige lys van hulpstowwe, sien afdeling 6.1.

3. FARMASEUTIESE VORM

Filmbedekte tablette.

TORQUIT 25 tablette is bruinerige rooi gekleurde, ronde, bikonvekse filmbedekte tablette, plein aan beide kante.
TORQUIT 100 tablette is wit tot naaswit, ronde, bikonvekse filmbedekte tablette en plein aan beide kante.
TORQUIT 200 tablette is wit tot naaswit, ronde, bikonvekse filmbedekte tablette met 'n breeklyn aan een kant en plein aan die ander kant.
TORQUIT 300 tablette is wit tot naaswit, kapsulevormige, bikonvekse filmbedekte tablette met 'n breeklyn aan beide kante.

Die **TORQUIT 200** en **TORQUIT 300** tablette kan in gelyke dosisse verdeel word.

4. KLINIESE BESONDERHEDE

4.1 Terapeutiese indikasies

TORQUIT is aangedui vir die behandeling van skisofrenie. TORQUIT word ook aangedui vir die behandeling van maniese episodes geassosieer met bipolêre steurings. Veiligheid en effektiwiteit langer as 12 weke is nie aangetoon nie.

4.2 Posologie en metode van toediening

Posologie
TORQUIT moet twee maal per dag, met of sonder voedsel toegedien word.

Volwassenes
Vir die behandeling van skisofrenie
Vir die behandeling van skisofrenie is die totale daaglikse dosis vir die eerste 4 dae van behandeling, 50 mg (Dag 1), 100 mg (Dag 2), 200 mg (Dag 3) en 300 mg (Dag 4).
Van Dag 4 af verder, moet die dosis getitreer word na die effektiewe dosisreikwydte van 300 - 450 mg/dag. Alhoewel, die dosis kan aangepas word op grond van die kliniese reaksie en verdraagsaamheid van die individuele pasiënt, binne die grense van 150 - 750 mg/dag.

Vir die behandeling van maniese episodes geassosieer met bipolêre steuring
Vir die behandeling van maniese episodes geassosieer met bipolêre steuring, is die totale daaglikse dosis vir die eerste 4 dae van terapie 100 mg (Dag 1), 200 mg (Dag 2), 300 mg (Dag 3) en 400 mg (Dag 4).
Verdere dosisaanpassings tot 800 mg/dag teen Dag 6 moet met inkremente van nie groter as 200 mg/dag wees nie.
Die dosis kan na gelang van die kliniese reaksie en verdraagsaamheid van die individuele pasiënt na tussen 200 - 800 mg/dag aangepas word. Die gewone effektiewe dosis is tussen die grense van 400 - 800 mg/dag.

Spesiale pasiëntgroepe:
Bejaardes
Soos met ander psigotika, moet TORQUIT met omsigtigheid by bejaardes gebruik word, in die besonder tydens die aanvanklike doseringstydperk.
Bejaarde pasiënte behoort met TORQUIT 25 mg/dag te begin. Die tempo van dosis titrasie mag wel stadiger moet wees, met inkremente van 25 - 50 mg, afhangend van die kliniese reaksie en verdraagsaamheid van die individuele pasiënt, na 'n effektiewe dosis, wat waarskynlik laer sal wees as dié by jonger pasiënte.

Renale en hepatiese inkorting
Die orale opruiming van TORQUIT is verminderde met ongeveer 25 % by pasiënte met renale of hepatiese inkorting. TORQUIT word omvattend gemetaboliseer deur die lewer, en moet dus met omsigtigheid gebruik word by pasiënte met bekende hepatiese inkorting.
Pasiënte met renale of hepatiese inkorting moet begin word met TORQUIT 25 mg/dag. Die dosis moet daagliks met inkremente van 25 - 50 mg verhoog word, tot 'n effektiewe dosis.

Pediatriese bevolking
Die veiligheid en effektiwiteit van TORQUIT by kinders en adolessente onder 18 jarige ouderdom is nie vasgestel nie.

Metode van toediening
Orale toediening.

4.3 Kontraïndikasies

- Hipersensitiwiteit teenoor die aktiewe substans of enige van die hulpstowwe gelys in afdeling 6.1.
- Swangerskap en laktasie, aangesien die veiligheid nie aangetoon is in hierdie populasie nie.
- Kinders en adolessente, aangesien die veiligheid nie aangetoon is in hierdie populasie nie.
- Gevorderde lewer- en renale funksie inkorting, aangesien die veiligheid nie aangetoon is nie.
- Gesamentlike toediening van sitochroom P450 3A4 inhibeerders, soos MIV-protease inhibeerders, asool-antifungus medisyne, eritromisien, klaritromisien en nefasodoon, is gekontraïndikeerd (sien afdeling 4.5).

4.4 Spesiale waarskuwings en voorsorgmaatreëls vir gebruik

Selfmoord/selfmoordgedagtes of kliniese verergering
Depressie word geassosieer met 'n verhoogde risiko van selfmoordgedagtes, selfbesering en selfmoord (selfmoordverwante gebeurtenisse). Hierdie risiko duur voort totdat daar beduidende remissie plaasvind. Aangesien verbetering nie gedurende die eerste paar weke of meer van behandeling mag plaasvind nie, moet pasiënte noukeurig gemonitor word totdat sulke verbetering plaasvind. Dit is algemene kliniese ervaring dat die risiko van selfmoord in die vroeë stadiums van herstel kan toeneem.

Daarbenewens moet mediese deskundiges die potensiële risiko van selfmoordverwante gebeurtenisse oorweeg na abrupte staking van TORQUIT behandeling, weens die bekende risikofaktore van die siekte wat behandel word.

Ander psigiatriese toestande waarvoor TORQUIT voorgeskryf word, kan ook met 'n verhoogde risiko van selfmoordverwante gebeurtenisse geassosieer word. Daarbenewens kan hierdie toestande ko-morbied wees met major depressiewe episodes. Dieselfde voorsorgmaatreëls wat waargeneem word by die behandeling van pasiënte met major depressiewe episodes, moet dus waargeneem word by die behandeling van pasiënte met ander psigiatriese afwykings.

Pasiënte met 'n geskiedenis van selfmoordverwante gebeurtenisse, of diegene wat 'n beduidende mate van selfmoordneigings voor die aanvang van behandeling toon, is bekend om 'n groter risiko vir selfmoordgedagtes of selfmoordpogings te hê, en moet noukeurig gemonitor word tydens behandeling.

Noukeurige toesig oor pasiënte en veral diegene met 'n hoë risiko moet die medikasie terapie vergesel, veral tydens vroeë behandeling en na dosisveranderings. Pasiënte (en versorgers van pasiënte) moet gewaarsku word oor die noodsaaklikheid om vir enige kliniese verergering te monitor, selfmoordgedrag of gedagtes en ongewone veranderinge in gedrag en om onmiddellik mediese advies te verkry indien hierdie simptome teenwoordig is.

In korter termyn plasebo-gekontroleerde kliniese studies van pasiënte met major depressiewe episodes van bipolêre steuring, is 'n verhoogde risiko vir selfmoordverwante gebeure waargeneem by jong volwasse pasiënte (jonger as 25 jarige ouderdom) wat behandel was met kwetiapien in vergelyking met dié wat behandel was met plasebo (3,0 % vs. 0 %, onderskeidelik). 'n Populasie-gebaseerde retrospektiewe studie van kwetiapien vir die behandeling van pasiënte met major depressiewe steuring het 'n verhoogde risiko vir selfbesering en selfmoord getoon by pasiënte van ouderdom 25 tot 64 jaar sonder 'n geskiedenis van selfbesering tydens die gebruik van kwetiapien saam met ander antidepressante.

Metaboliese risiko
Gegewe die waargenome risiko vir verergering van hul metaboliese profiel, insluitend veranderinge in gewig, bloedglukose (sien hiperglisemie) en lipiede, wat in kliniese studies gesien is, moet pasiënte se metaboliese parameters geassesseer word by die aanvang van behandeling en veranderinge in hierdie parameters moet gereeld gekontroleer word vir die duur van die kursus van behandeling. Verergering in hierdie parameters moet bestuur word soos kliniese toepaslik (sien ook afdeling 4.8).

Tardiewe diskinesie en ekstrapiramidale simptome
Daar is 'n potensiaal dat TORQUIT tardiewe diskinesie kan veroorsaak. Indien tekens en simptome van tardiewe diskinesie verskyn, moet dosisverlaging of staking van TORQUIT oorweeg word. Die simptome van tardiewe diskinesie kan vererger of selfs ontstaan na staking van behandeling. (sien afdeling 4.8).
In plasebo-gekontroleerde kliniese toetse van volwasse pasiënte met skisofrenie en bipolêre manie was die voorkoms van ekstrapiramidale simptome nie anders as dié van plasebo oor die aanbevole terapeutiese dosisreeks nie.
In plasebo-gekontroleerde kliniese toetse van volwasse pasiënte, is kwetiapien geassosieer met 'n verhoogde voorkoms van ekstrapiramidale simptome (EPS) in vergelyking met plasebo by pasiënte wat behandel was vir major depressiewe episodes in bipolêre steuring (sien afdeling 4.8).
Die gebruik van kwetiapien is geassosieer met die ontwikkeling van akatisie, wat gekenmerk word deur 'n subjektiewe onaangename of kommerwekkende rusteloosheid en behoefte om dikwels te beweeg gepaardgaande met 'n onvermoë om te sit of stil te staan. Dit sal waarskynlik binne die eerste paar weke van behandeling plaasvind. By pasiënte waar hierdie simptome ontwikkel, kan dosis verhoging nadelig wees.

Somnolensie en duiseligheid
Kwetiapien behandeling is geassosieer met somnolensie en verwante simptome, soos sedasie (sien afdeling 4.8).
Vir die behandeling van pasiënte met bipolêre depressie, was dit gedemonstreer dat die aanvang normaalweg binne die eerste 3 dae van behandeling was en was hoofsaaklik van ligte tot matige intensiteit. Pasiënte wat somnolensie van 'n erge intensiteit ervaar mag dalk meer gereelde kontak benodig vir 'n minimum van 2 weke vanaf die aanvang van somnolensie, of totdat simptome verbeter en staking van behandeling mag dalk oorweeg moet word.

Ortostatiese hipotensie
Kwetiapien behandeling is geassosieer met ortostatiese hipotensie en verwante duiseligheid (sien afdeling 4.8) wat soos somnolensie gewoonlik voorkom gedurende die aanvanklike dosis-titrasietydperk. Dit kan die voorkoms van toevallige beserings (val) verhoog, veral by die bejaarde populasie. Daarom moet pasiënte ingelig word om versigtig te wees totdat hul vertroud is met die moontlike effekte van die medisyne.
Kwetiapien moet met omsigtigheid gebruik word by pasiënte met bekende kardiovaskulêre siekte, serebrovaskulêre siekte, of ander toestande wat tot hipotensie aanleiding kan gee. Dosisvermindering of meer geleidelike titrasie moet oorweeg word indien ortostatiese hipotensie plaasvind, veral by pasiënte met onderliggende kardiovaskulêre siekte.

Slaapapnee sindroom
Slaapapnee sindroom is aangemeld by pasiënte wat kwetiapien gebruik. By pasiënte wat gelyktydig sentralesenuisteem depressante ontvang en wat 'n geskiedenis het van of op risiko is vir slaapapnee, soos diegene wat oorgewig/vetsugtig of manlik is, moet TORQUIT met omsigtigheid gebruik word.

Stuipe
Daar is aangetoon dat daar geen verskil is in die voorkoms van stuipe by pasiënte wat met kwetiapien of plasebo behandel was nie. Geen data is beskikbaar oor die voorkoms van stuipe by pasiënte met 'n geskiedenis van stuipsversteuring nie. Soos met ander antipsigotika, word omsigtigheid aanbeveel wanneer pasiënte met 'n geskiedenis van stuipe behandel word (sien afdeling 4.8).

Neuroleptiese kwaadaardige sindroom
Neuroleptiese kwaadaardige sindroom is geassosieer met antipsigotiese behandeling, insluitend kwetiapien (sien afdeling 4.8). Kliniese manifestasies sluit in hipertermie, veranderde geestestoestand, spierrigiditeit, outonome onstabiliteit, en verhoogde kreatienfosfokinase. In so 'n geval moet kwetiapien gestaak word en die gepaste mediese behandeling gegee word.

Erge neutropenie en agranulositose
Erge neutropenie (neutrofieltelling < 0,5 x 109/L) sonder infeksie is in kwetiapien kliniese studies aangemeld. Daar was verslae van agranulositose (erge neutropenie met infeksie) onder alle pasiënte wat met kwetiapien behandel was, soos bevat in TORQUIT, tydens kliniese studies sowel as in na-bemarkingsverslae. Die meeste gevalle van erge neutropenie het binne die eerste twee maande na die aanvang van die behandeling met kwetiapien voorgekom. Daar was geen oënskynlike dosisverhouding nie. Tydens na-bemarkingservaring was sommige gevalle dodelik. Moontlike risikofaktore vir neutropenie sluit in die reeds bestaande lae witbloedseltelling (WBS) en geskiedenis van medisyne-geïnduseerde neutropenie. Daar was gevalle by pasiënte sonder voorafgaande risikofaktore. Neutropenie moet oorweeg word by pasiënte wat met infeksie presenteer, veral in die afwesigheid van ooglopende predisponerende faktor(e), of by pasiënte met onverklaarbare koors, en dit moet kliniese toepaslik bestuur word. Kwetiapien moet gestaak word by pasiënte met 'n neutrofieltelling < 1,0 x 109/L. Pasiënte moet geobserveer word vir tekens en simptome van infeksie en neutrofieltelling moet gedoen word (totdat hulle 1,5 x 109/L oorskry) (sien afdeling 5.1).
Pasiënte moet aangeraai word om die voorkoms van tekens/simptome wat ooreenstem met agranulositose of infeksie (bv. koors, swakheid, lusteloosheid of keelseer) onmiddellik te rapporteer ter eniger tyd tydens TORQUIT terapie. By sulke pasiënte moet 'n WBS telling en 'n absolute neutrofieltelling (ANT) vinnig uitgevoer word, veral in die afwesigheid van predisponerende faktore.

Antikolinergiese (muskariene) effekte
Norkwetiapien, 'n aktiewe metaboliet van kwetiapien, het matige tot sterk affiniteit vir verskillende muskariniese reseptor subtipes. Dit dra by tot die ongewenste reaksies wat antikolinergiese effekte weerspieël wanneer kwetiapien in aanbevole dosisse gebruik word, wanneer dit saam met ander medikasie gebruik word wat antikolinergiese effekte het, en met oordosis.
TORQUIT moet met omsigtigheid gebruik word by pasiënte wat medisyne ontvang wat antikolinergiese (muskariene) effekte het.
TORQUIT moet met omsigtigheid gebruik word by pasiënte met 'n huidige diagnose of vorige geskiedenis van urienretensie, kliniese beduidende prostaat hipertrofie, intestinale obstruksie of verwante toestande, verhoogde intra-okulêre druk of nouhoek gloukoom (sien afdeling 4.5, afdeling 4.8, afdeling 5.1 en afdeling 4.9).

Interaksies
Sien afdeling 4.5.
Gelyktydige gebruik van kwetiapien en 'n sterk hepatiese ensieminduseerder soos karbamasepien of fenitoïen verlaag kwetiapien plasmakonsentrasies aansienlik, wat die effektiwiteit van TORQUIT terapie kan beïnvloed. By pasiënte wat 'n hepatiese ensieminduseerder ontvang, moet die inisiëring van TORQUIT behandeling slegs plaasvind indien die mediese deskundige van mening is dat die voordele van kwetiapien die risiko's om die hepatiese-ensieminduseerder te verwyder, oortref. Dit is belangrik dat enige veranderinge in die induseerder geleidelik moet wees, en indien nodig, vervang word met 'n nie-induseerder (bv. natriumvalproaat).

Gewig
Gewigstoename is aangemeld by pasiënte wat met kwetiapien behandel word, en moet gemonitor en bestuur word soos klinies toepaslik, in ooreenstemming met die gebruikte antipsigotiese riglyne (sien afdeling 4.8 en afdeling 5.1).

Hiperglisemie en diabetes mellitus
Hiperglisemie, in sommige gevalle uitermate en geassosieer met ketoasidose of hiperosmolare koma of die dood, is aangemeld by pasiënte wat met kwetiapien, soos bevat in TORQUIT, behandel is (sien afdeling 4.8). In sommige gevalle is 'n voorafgaande toename in liggaamsgewig gerapporteer, wat 'n predisponerende faktor kan wees. Toepaslike kliniese monitering word aanbeveel in ooreenstemming met die gebruikte antipsigotiese riglyne.
Pasiënte met 'n bevestigde diagnose van diabetes mellitus wat met TORQUIT begin, moet gereeld gemonitor word vir agteruitgang van glukosebeheer. Pasiënte met risikofaktore vir diabetes mellitus (bv. obesiteit, familiegeskiedenis van diabetes) wat behandeling met TORQUIT begin, moet gemonitor word vir simptome van hiperglisemie insluitend polidipsie, poliurie, polifagie, en swakheid. Pasiënte wat simptome van hiperglisemie ontwikkel tydens behandeling met kwetiapien, moet vastende bloedglukosetoetsing ondergaan. In sommige gevalle het hiperglisemie opgeklaar toe TORQUIT gestaak is; alhoewel, sommige pasiënte het egter voortsetting van antidiabetiese behandeling benodig ondanks staking van die geneesmiddel waaroor daar onsekerheid is.

Lipiede
Verhogings in trigliseriede, laedigtheidslipoproteïene (LDL) en totale cholesterol, en afname in hoëdigtheidslipoproteïene (HDL) cholesterol is waargeneem in kliniese proewe met kwetiapien (sien afdeling 4.8). Lipiedveranderings moet as klinies toepaslik bestuur word.

QT-verlenging
In kliniese proewe en gebruik in ooreenstemming met die SPC, was kwetiapien nie geassosieer met 'n aanhoudende toename in absolute QT-intervalle nie. Na-bemarking is QT-verlenging met kwetiapien gerapporteer by die terapeutiese dosisse (sien afdeling 4.8) en in oordosis (sien afdeling 4.9). Omsigtigheid word aanbeveel wanneer TORQUIT voorgeskryf word by pasiënte met kardiovaskulêre siekte of familiegeskiedenis van QT-verlenging. Omsigtigheid moet ook toegepas word as TORQUIT voorgeskryf word, hetsy met medisyne wat bekend is dat dit QT-interval verhoog, of met gepaardgaande neuroleptika, veral by bejaardes, by pasiënte met kongenitale lang QT-sindroom, kongestiewe hartversaking, harthipertrofie, hipokalemie of hipomagnesemie (sien afdeling 4.5).

Kardiomiopatie en miokarditis
Kardiomiopatie en miokarditis is aangemeld in kliniese proewe en tydens na-bemarkingservaring. Behandeling met kwetiapien moet heroorweeg word by pasiënte met vermoedelike kardiomiopatie of miokarditis.

Onttrekking
Akute onttrekkingsimptome, soos slapeloosheid, naarheid, hoofpyn, diarree, braking, duiseligheid en prikkelbaarheid is beskryf na die skielike staking van kwetiapien. Geleidelike onttrekking oor 'n tydperk van minstens een tot twee weke is raadsaam (sien afdeling 4.8).

Bejaarde pasiënte met demensie-verwante psigose
TORQUIT is nie goedgekeur vir die behandeling van demensie-verwante psigose nie.
In 'n meta-analise van atipiese antipsigotika, is dit berig dat bejaarde pasiënte met demensie-verwante psigose 'n groter risiko vir dood het in vergelyking met plasebo. In twee 10-week plasebo-gekontroleerde kwetiapien studies in dieselfde pasiënt populasie (n=710); gemiddelde ouderdom: 83 jaar; gebied: 56 - 99 jaar) was die insidens van mortaliteit in kwetiapien behandelde pasiënte 5,5 % teenoor 3,2 % in die plasebo groep. Die pasiënte in hierdie proewe het gesterf van 'n verskeidenheid oorsake wat konsekwent is met verwagtinge vir hierdie populasie.

Bejaarde pasiënte met Parkinson se siekte (PS)/parkinsonisme
'n Bevolking-gebaseerde retrospektiewe studie van kwetiapien vir die behandeling van pasiënte met major depressiewe steuring, het 'n verhoogde risiko van sterfte getoon tydens die gebruik van kwetiapien by pasiënte van > 65 jaar. Hierdie assosiasie was nie teenwoordig toe pasiënte met PS uit die ontleding verwyder was nie. Omsigtigheid moet toegepas word indien kwetiapien voorgeskryf word aan bejaarde pasiënte met PS.

Disfagie
Disfagie (sien afdeling 4.8) is aangemeld met kwetiapien. TORQUIT moet met omsigtigheid gebruik word by pasiënte met 'n risiko vir aspirasielongontsteking.

Konstipasie en intestinale obstruksie
Konstipasie verteenwoordig 'n risikofaktor vir intestinale obstruksie. Konstipasie en intestinale obstruksie is aangemeld met kwetiapien (sien afdeling 4.8). Dit sluit in dodelike verslae by pasiënte wat 'n hoër risiko vir intestinale obstruksie het, insluitend diegene wat veelvuldige gelyktydige medikasie ontvang wat die intestinale motiliteit verminder en/of nie simptome van hardlywigheid aanmeld nie. Pasiënte met intestinale obstruksie/ileus moet met noukeurige monitering en dringende sorg bestuur word.

Veneuse trombo-embolisme (VTE)
Gevalle van veneuse trombo-embolisme (VTE) is aangemeld met antipsigotiese medisyne. Aangesien pasiënte wat behandel word met antipsigotika, insluitend TORQUIT, dikwels met verworwe risikofaktore vir VTE voorkom, moet alle moontlike risikofaktore vir VTE geïdentifiseer word voor en tydens behandeling met kwetiapien en voorkomende maatreëls moet geneem word.

Pankreatitis
Pankreatitis is in kliniese proewe en tydens na-bemarkingservaring aangemeld. In na-bemarkingsverslae, alhoewel nie alle gevalle met risikofaktore verband gehou het nie, het baie pasiënte faktore gehad wat bekend is dat dit geassosieer word met pankreatitis, soos verhoogde trigliseriede, galstene en alkoholverbruik.

Addisionele informasie
Kwetiapiendata in kombinasie met divalproeks of litium in akute matige tot ernstige maniese episodes is beperk; alhoewel, kombinasieterapie goed verdra was (sien afdeling 4.8 en afdeling 5.1). Die data het 'n bydraende effek teen week 3 getoon.

Misbruik
Gevalle van misbruik is aangemeld. Omsigtigheid word aanbeveel wanneer TORQUIT voorgeskryf word aan pasiënte met 'n geskiedenis van alkohol- of dwelmmisbruik.

Pediatriese populasie
TORQUIT word nie aanbeveel vir gebruik by kinders en adolessente onder 18 jarige ouderdom nie, weens 'n gebrek aan data om die gebruik in hierdie ouderdomsgroep te ondersteun. Kliniese proewe met kwetiapien het getoon dat benewens die bekende veiligheidsprofiel wat by volwassenes geïdentifiseer is (sien afdeling 4.8), sekere ongewenste gebeure op 'n hoër frekwensie by kinders en adolessente plaasgevind het in vergelyking met volwassenes (verhoogde eetlus, toename in serumprolaktien, braking, rinitis en sinkope), of mag verskillende implikasies vir kinders en adolessente hê (ekstrapiramidale simptome en prikkelbaarheid) en een was geïdentifiseer wat nie voorheen in volwasse studies gesien was nie (toename in bloeddruk). Veranderings in tiroïedfunksietoetse is ook by kinders en adolessente waargeneem.

Daarbenewens, die langtermyn veiligheidsimplikasies van behandeling met kwetiapien op groei en rypwording is vir nie langer as 26 weke bestudeer nie. Langtermynimplikasies vir kognitiewe- en gedragsontwikkeling is nie bekend nie.
In plasebo-gekontroleerde kliniese proewe met kinders en adolessente pasiënte, was kwetiapien geassosieer met 'n verhoogde voorkoms van ekstrapiramidale simptome (EPS) in vergelyking met plasebo by pasiënte wat behandel was vir skisofrenie, bipolêre manie of bipolêre depressie (sien afdeling 4.8).

Laktose
TORQUIT tablette bevat laktose. Pasiënte met die seldsame oorerflike toestande van galaktose-onverdraagsaamheid, bv. galaktosemie, Lapp laktase-tekort, glukose-galaktose wanabsorpsie of fruktose-onverdraagsaamheid moet met hul dokter of apteker praat voordat TORQUIT geneem word.
Die klein hoeveelheid laktose in elke dosis sal waarskynlik nie simptome veroorsaak by volwassenes met laktose-onverdraagsaamheid nie.

4.5 Interaksie met ander medisyne en ander vorms van interaksie

Gegewe die primêre sentrale senuweestelsel effekte van kwetiapien, moet TORQUIT met omsigtigheid gebruik word in kombinasie met ander sentraalwerkende medisinale produkte en alkohol.

Omsigtigheid moet beoefen word met behandeling van pasiënte wat ander medisyne met anti-cholinergiese (muskariene) effekte ontvang (sien afdeling 4.4).

Sitochrome P450 (CYP) 3A4 is die ensiem wat hoofsaaklik verantwoordelik is vir die sitochroom P450-gemedieerde metabolisme van kwetiapien. In 'n interaksie-studie by gesonde vrywilligers het die gelyktydige toediening van kwetiapien (dosis van 25 mg) met ketokonasool, 'n CYP3A4-inhibeerder, 'n 5- tot 8-voudige toename in die AOK van kwetiapien veroorsaak. Op grond hiervan is die gelyktydige gebruik van kwetiapien en CYP3A4-inhibeerder gekontraïndikeerd. Dit word ook nie aanbeveel om pomelo sap te neem tydens kwetiapienterapie nie.

Kwetiapien het nie die lewerensiemsisteem betrokke by die metabolisme van antipirien geïnduseer nie. In 'n meervoudige-dosisproef by pasiënte om die farmakokinetika van kwetiapien wat voor en tydens behandeling met karbamasepien gegee is ('n bekende hepatiese ensieminduseerder) te beoordeel, het die gesamentlike toediening van karbamasepien die opruiming van kwetiapien aansienlik verhoog. Hierdie toename in opruiming het sistemiese blootstelling van kwetiapien verminder (soos gemeet deur AOK) tot 'n gemiddeld van 13 % van die blootstelling tydens toediening van kwetiapien alleen; alhoewel 'n groter effek was gesien by sommige pasiënte. As gevolg van hierdie interaksie kan laer plasmakonsentrasies voorkom, wat die effektiwiteit van kwetiapienterapie kan beïnvloed. Gelyktydige toediening van kwetiapien en fenitoïen ('n ander mikrosomale ensieminduseerder) het 'n aansienlike verhoogde opruiming van kwetiapien veroorsaak van ongeveer 450 %. By pasiënte wat 'n hepatiese ensieminduseerder ontvang, moet die inisiëring van TORQUIT behandeling slegs plaasvind indien die mediese deskundige van mening is dat die voordele van kwetiapien die risiko's om die hepatiese-ensieminduseerder te verwyder, oortref. Dit is belangrik dat enige veranderinge in die induseerder geleidelik moet wees, en indien nodig, vervang word met 'n nie-induseerder (bv. natriumvalproaat) (sien afdeling 4.4).

CYP3A4 is die primêre ensiem verantwoordelik vir sitochroom P450-gemedieerde metabolisme van kwetiapien (soos in TORQUIT). Die farmakokinetika van kwetiapien was nie verander na gesamentlike toediening met simetidien, 'n bekende P450-ensieminhibeerder, nie. Die farmakokinetika van kwetiapien (soos in TORQUIT) was nie beduidend verander na gesamentlike toediening met die antidepressante imipramien ('n bekende CYP2D6-inhibeerder) of fluoksetien ('n bekende CYP3A4- en CYP2D6-inhibeerder) nie. In 'n meervoudige-dosisproef by gesonde vrywilligers om die farmakokinetika van kwetiapien (soos in TORQUIT) te beoordeel, toegedien voor en tydens behandeling met ketokonasool, het gesamentlike toediening van ketokonasool gelei tot 'n toename in die gemiddelde Kmaks en AOK van kwetiapien (soos in TORQUIT) van 235 % en 522 %, onderskeidelik, met 'n ooreenstemmende afname in gemiddelde orale klaring van 84 %. Die gemiddelde halfleeftyd van kwetiapien (soos in TORQUIT) het van 2,6 tot 6,8 uur toegeneem, maar die gemiddelde tmaks was onveranderd.

Die farmakokinetika van kwetiapien was nie beduidend verander deur gelyktydige toediening van die antipsigotika risperidoon of haloperidol nie. Gelyktydige gebruik van kwetiapien en tioridasien het 'n verhoogde opruiming van kwetiapien veroorsaak van ongeveer 70 %.

Die farmakokinetika van litium was nie verander met gelyktydige toediening met kwetiapien (soos in TORQUIT) nie.

Die farmakokinetika van natriumvalproaat en kwetiapien (soos in TORQUIT) was nie in 'n kliniese relevante mate verander met gelyktydige toediening nie.

Omsigtigheid moet toegepas word wanneer TORQUIT gelyktydig gebruik word met medisinale produkte bekend om elektrolietwanbalans of verhoogde QT-interval te veroorsaak.

Daar was berigte van vals positiewe resultate in ensiem-immuno toetse vir metadoon- en trisikliese antidepressante by pasiënte wat kwetiapien geneem het. Bevestiging van twyfelagtige immuno toets siftings resultate deur 'n geskikte chromatografiese tegniek word aanbeveel.

4.6 Vrugbaarheid, swangerskap en borsvoeding

Swangerskap
TORQUIT is gekontraïndikeerd vir die gebruik tydens swangerskap, aangesien die veiligheid nie aangetoon is nie (sien afdeling 4.3).

Borsvoeding
TORQUIT is gekontraïndikeerd vir die gebruik tydens laktasie , aangesien die veiligheid nie aangetoon is nie (sien afdeling 4.3).

Vrugbaarheid
Geen data oor manlike of vroulike vrugbaarheid is beskikbaar nie.

4.7 Uitwerking op die vermoë om te bestuur en masjiene te gebruik

TORQUIT kan somnolensie veroorsaak, wat kan inmeng met aktiwiteite wat verstandelike helderheid vereis. Pasiënte moet dus aangeraai word om nie 'n voertuig te bestuur of met masjinerie te werk nie, totdat individuele vatbaarheid bekend is. Dit is nie altyd moontlik om te voorspel in watter mate TORQUIT die daaglikse aktiwiteite van 'n pasiënt kan beïnvloed nie. Pasiënte moet toesien dat hulle nie aan bogenoemde aktiwiteite deelneem totdat hulle bewus is van die mate waarop TORQUIT hulle beïnvloed nie.

4.8 Newe-effekte

a. Opsomming van die veiligheidsprofiel
Die algemeenste ongewenste reaksies (OMR) met kwetiapien (≥ 10 %) is somnolensie, duiseligheid, hoofpyn, droë mond, onttrekkings (staking) simptome, verhogings in serum trigliseriedvlakke, verhogings in totale cholesterol (oorwegend LDL cholesterol), afname in HDL cholesterol, gewigstoename, verminderde hemoglobien en ekstrapiramidale simptome.
Ander ongewenste effekte sluit in droë mond, astenie, konstipasie, tagikardie, ortostatiese hipotensie en dispepsie.

Sinkopee, kwaadaardige neuroleptiese sindroom, leukopenie, neutropenie en perifere edeem, is geassosieer met kwetiapien soos in TORQUIT.

b. Getabuleerde opsomming van newe-effekte

Sisteem-orgaanklas	Frekwensie	Ongewenste effekte
Bloed- en die limfstelselversteurings	Gereeld	Verlaagde neutrofieltelling, verlaagde
	Minder gereeld	Agranulositose[26], anemie, neutropenie[1], verlaagde plaatjietelling[13], trombositopenie.
Immuunstelsel versteurings	Minder gereeld	Anafilaktiese reaksies[5], hipersensitiwiteit (insluitend allergiese veltoestande).
Endokriene versteurings	Gereeld	Hiperprolaktinemie[15], Verlaging in totale T4[24], verlaging in vry T4[24], verlaging in totale T3[24], verhoging in TSH[24].
	Minder gereeld	Verlaging in vry T3[24], hipotiroïdisme[21], onvanpaste antidiuretiese hormoonsekresie.
Metabolisme- en voedingsversteurings	Gereeld	Bloedglukose verhoging na hiperglisemiese vlakke[6, 30], verlaging in HDL cholesterol[17,30], verhogings in serum trigliseriedvlakke[10,30],
	Minder gereeld	Diabetes mellitus[1,5], vererging van bestaande diabetes, hiponatremie[19], metaboliesesindroom[29].
Psigiatriese versteurings	Gereeld	Abnormale drome en nagmerries, selfmoordneigings en selfmoordgedrag[20].
	Minder gereeld	Somnambulisme en verwante reaksies soos slaappraatjies en slaapverwante eetversteuring.
Senustelselversteurings	Gereeld	Duiseligheid[4,16], disartrie, ekstrapiramidale simptome[1, 21], hoofpyn, somnolensie[2,16].
	Minder gereeld	Rustelose bene sindroom, stuipe[1], sinkopee[4,16], tardiewe diskinesie[1, 5].
Oogversteurings	Gereeld	Versteurde visie.
Hartversteurings	Gereeld	Palpitasies[23], tagikardie[4].
	Minder Gereeld	Bradikardie[32], QT-verlenging [1,12,18].
Vaskulêre versteurings	Gereeld	Ortostatiese hipotensie[4,16].
	Minder gereeld	Beroerte[33], veneuse trombo-embolie[1].
Respiratoriese, torakale- en mediastinale versteurings	Gereeld	Dispnee[23].
	Minder gereeld	Rinitis.
Gastro-intestinale versteurings	Gereeld	Konstipasie, droë mond, dispepsie, braking[25].
	Minder gereeld	Disfagie[7], intestinale obstruksie/Ileus, pankreatitis[1].
Hepato-biliêre versteurings	Gereeld	Verhogings in gamma-GT vlakke[3], verhogings in serum alanien aminotransferase (ALT)[3].
	Minder gereeld	Verhogings in serum aspartaat aminotransferase (AST)[3], hepatitis, geelsug[5].
Vel- en Onderhuidse weefselversteurings	Minder gereeld	Angioedeem[5], medisyne uitslag met eosinofilie en sistemiese simptome (MUESS), eriteem multiforme, Stevens- Johnson sindroom[5], toksiese epidermale nekrolise.
Muskuloskeletale bindweefselversteurings	Minder gereeld	Rabdomiolise.
Renale en urinêre versteurings	Minder gereeld	Urinêre retensie.
Swangerskap, puerperium en perinatale toestande	Minder gereeld	Medisyne onttrekkingsindroom neonataal[31]
Voorplantingstelsel- en borsversteurings	Minder gereeld	Bors swelling, galaktorree, menstruele versteuring, priapisme, seksuele disfunksie.
Algemene versteurings en toedieningsplektoestande	Gereeld	Prikkelbaarheid, matige astenie, perifere edeem, pireksie, onttrekking (staking) simptome[1,9].
	Minder gereeld	Kwaadaardige neuroleptiese sindroom[1], hipotermie.
	Frekwensie onbekend	Neonatale onttrekking.
Ondersoeke	Minder gereeld	Verhogings in bloed kreatienfosfokinase[14].

1. Sien afdeling 4.4.
2. Somnolensie mag plaasvind, gewoonlik tydens die eerste twee weke van behandeling en los gewoonlik op met die voortgesette toediening van kwetiapien.
3. Asimptomatiese verhogings (skuif van normaal na >3 x BLN ter eniger tyd) in serum transaminase (ALT, AST) of gamma-GT vlakke is waargeneem in sommige pasiënte toegedien met kwetiapien. Hierdie verhogings was normaalweg omkeerbaar met voortgesette kwetiapien behandeling.
4. Soos met ander antipsigotika met alfa1 adrenergiese blokkeringsaktiwiteit, kan kwetiapien gewoonlik ortostatiese hipotensie veroorsaak, geassosieer met duiseligheid, tagikardie en, by sommige pasiënte, sinkopee, veral gedurende die aanvanklike dosis-titrasietydperk (sien afdeling 4.4).
5. Berekening van frekwensie van hierdie ADR's is geneem slegs vanaf na-bemarkingsdata alleenlik.
6. Vastende bloedglukose ≥ 126 mg/dL (≥ 7,0 mmol/L) of 'n nie-vastende bloedglukose ≥ 200 mg/dL (≥ 11,1 mmol/L) op ten minste een geleentheid.
7. 'n Toename in die tempo van disfagie met kwetiapien teenoor plasebo was slegs waargeneem in die kliniese proewe van bipolêre depressie.
8. Gebaseer op > 7 % verhoging in liggaamsmassa van basislyn. Vind hoofsaaklik plaas tydens die vroeë weke van behandeling in volwassenes.
9. Die volgende onttrekkingsimptome was meer gereeld waargeneem in akute plasebo-gekontroleerde, monoterapie kliniese proewe, wat stakings simptome verhoog het: slaaploosheid, naarheid, hoofpyn, diarree, braking, duiseligheid, en prikkelbaarheid. Die voorkoms van hierdie reaksies het aansienlik afgeneem na 1 week na-staking.
10. Trigliseriede ≥ 200 mg/dL (≥ 2,258 mmol/L) (pasiënte ≥ 18 jarige ouderdom) of ≥ 150 mg/dL (≥ 1,694 mmol/L) (pasiënte < 18 jarige ouderdom) op ten minste een geleentheid.
11. Cholesterol ≥ 240 mg/dL (≥ 6,2064 mmol/L) (pasiënte ≥ 18 jarige ouderdom) of ≥ 200 mg/dL (≥ 5,172 mmol/L) (pasiënte < 18 jarige ouderdom) op ten minste een geleentheid. 'n Verhoging in LDL cholesterol van ≥ 30 mg/dL (≥ 0,769 mmol/L) is algemeen waargeneem. Gemiddelde verandering tussen pasiënte wat hierdie verhoging getoon het was 41,7 mg/dL (≥ 1,07 mmol/L).
12. Sien onderstaande teks.
13. Plaatjies ≤ 100 x 109/L op ten minste een geleentheid.
14. Op grond van kliniese proef nadelige-insidentverslae van bloed kreatienfosfokinase toename hou dit nie verband met kwaadaardige neuroleptiese sindroom nie.
15. Prolaktienvlakke (pasiënte >18 jarige ouderdom): > 20 μg/L (> 869,56 pmol/L) mans; > 30 μg/L (> 1304,34 pmol/L) vroue ter eniger tyd.
16. Kan lei tot val.
17. HDL cholesterol: < 40 mg/dL (1,025 mmol/L) mans; < 50 mg/dL (1,282 mmol/L) vroue ter eniger tyd.
18. Voorkoms van pasiënte met 'n QTc skuif van < 450 msek tot ≥ 450 msek met 'n ≥ 30 msek verhoging. In plasebo-gekontroleerde proewe met kwetiapien was die gemiddelde verandering en die voorkoms van pasiënte wat na 'n klinies beduidende vlak verskuif, soortgelyk tussen kwetiapien en plasebo.
19. Skuif van > 132 mmol/L na ≤ 132 mmol/L op ten minste een geleentheid.
20. Gevalle van selfmoordgedagtes en selfmoordgedrag is tydens kwetiapienterapie of vroeg na staking van die behandeling aangemeld (sien afdeling 4.4 en afdeling 5.1).
21. Sien afdeling 5.1.
22. Verlaagde hemoglobien tot ≤ 13 g/dL (8,07 mmol/L) mans, ≤ 12 g/dL (7,45 mmol/L) vrouens op ten minste een geleentheid het by 11 % van die kwetiapienpasiënte voorgekom in alle proewe, insluitend oop-etiketuitbreidings. Vir hierdie pasiënte was die gemiddelde maksimum verlaging in hemoglobien te eniger tyd – 1,50 g/dL.
23. Hierdie verslae het gereeld voorgekom in die stelling van tagikardie, duiseligheid, ortostatiese hipotensie en/of onderliggende kardiale/respiratoriese siekte.
24. Gebaseer op verskuiwings van normale basislyn na potensieel kliniese belangrike waarde te eniger tyd na-basislyn in alle proewe.
Verskuiwings in totale T_4, vrye T_4, totale T_3 en vrye T_3 word gedefinieer as < 0,8 x LLN (pm/L) en die verskuiwing in TSH is te eniger tyd > 5 mIU/L.
25. Gebaseer op die verhoogde gevalle van braking by ouer pasiënte (≥ 65 jarige ouderdom).
26. Gebaseer op die verskuiwing in neutrofiele van > = 1,5 x 109L basislyn na < 0,5 x 109/L te eniger tyd tydens behandeling en gebaseer op pasiënte met ernstige neutropenie (< 0,5 x 109/L) en infeksie tydens alle kwetiapien kliniese proewe (sien afdeling 4.4).
27. Gebaseer op verskuiwings van normale basislyn na potensieel kliniese belangrike waarde te eniger tyd na-basislyn in alle proewe. Verskuiwings in eosinofiele word gedefinieer as > 1 x 109 selle/L ter eniger tyd.
28. Gebaseer op verskuiwings van normale basislyn na potensieel kliniese belangrike waarde te eniger tyd na-basislyn in alle proewe. Verskuiwings in WBSe word gedefinieer as ≤ 3 x 109 selle/L te eniger tyd.
29. Gebaseer op nadelige gevalverslae van metaboliese sindroom van alle kliniese proewe met kwetiapien.
30. In sommige pasiënte is 'n verergering van meer as een van die metaboliese faktore van gewig, bloedglukose en lipiede in kliniese studies waargeneem (sien afdeling 4.4).
31. Sien afdeling 4.3 en 4.6 – TORQUIT is gekontraïndikeerd in swangerskap.
32. Mag voorkom met of naby die aanvang van die behandeling en geassosieer word met hipotensie en/of sinkopee. Frekwensie gebaseer op nadelige gevalverslae van bradikardie en verwante gevalle in alle kliniese proewe met kwetiapien.
33. Gebaseer op een retrospektiewe nie-gerandomiseerde epidemiologiese studie.
Gevalle van QT verlenging, ventrikulêre aritmie, skielike onverklaarbare dood, hartstilstand en torsades de pointes is aangemeld met die gebruik van neuroleptika en word as klaseffekte beskou.
Ernstige kutane nadelige-reaksies (EKNRs), insluitend Stevens-Johnson-sindroom (SJS), toksiese epidermale nekrolise (TEN) medisyne-reaksie met eosinofilie en sistemiese simptome (MUESS) is aangemeld in assosiasie met kwetiapien behandeling.

c. Beskrywing van geselekteerde newe-effekte
TORQUIT behandeling was geassosieer met dosisverwante afnames in tiroïedhormoonvlakke, veral totale T4 en vrye T4. Die afname in totale en vrye T4 was maksimaal binne die eerste 2 tot 4 weke van TORQUIT behandeling, met geen verdere afnames tydens langtermynbehandeling nie. Daar was geen bewyse van klinies beduidende veranderinge in die TSH-konsentrasie met tyd nie. In bykans alle gevalle was staking van TORQUIT-behandeling geassosieer met die omkeer van die effekte op totale en vrye T4, ongeag die duur van die behandeling. Kleiner afnames in totale T3 en omgekeerde T3 is slegs by hoër dosisse waargeneem. TBG-vlakke was onveranderd en oor die algemeen, is resiprokale toenames in TSH nie waargeneem nie, met geen aanduiding dat kwetiapien (soos in TORQUIT) klinies relevante hipotiroïdisme veroorsaak nie.

Die volgende newe-effekte wat in kliniese proewe waargeneem is, is nie medisyneverwant nie en die frekwensie daarvan is onbekend: hoofpyn, abdominale pyn, rugpyn, borspyn, hipertensie, diarree, mialgie, angs, droë oë, oorpyn en urienweginfeksie.

Ekstrapiramidale simptome (akatisie, akinesie, tandratrigiditeit, ekstrapiramidale sindroom, hipertonie, hipokinesie, nekrigiditeit en tremor) kom voor by 'n voorkoms soortgelyk aan plasebo en is nie dosisverwant nie.

TORQUIT kan verlenging van die QTc interval veroorsaak (sien afdeling 4.4).

Rapportering van vermoedelike newe-effekte
Dit is belangrik om vermoedelike newe-effekte wat waargeneem word nadat die medisyne goedgekeur is, te rapporteer. Dit laat volgehoue observering van die voordeel/risiko-balans van die medisyne toe. Gesondheidsorgverskaffers word versoek om enige vermoedelike newe-effekte aan SAHPRA te rapporteer via die "6.04 Adverse Drug Reactions Reporting Form", wat aanlyn by SAHPRA se publikasies gevind kan word: https://www.sahpra.org.za/Publications/Index/8.

4.9 Oordosering

Simptome
In kliniese proewe is die ervaring met kwetiapien (soos in TORQUIT) met oordosering beperk. In na-bemarkingservaring was daar baie seldsame verslae van oordosering van kwetiapien alleen wat gelei het tot dood of koma.
Oor die algemeen was aangemelde tekens en simptome, dié wat voortgespruit het uit 'n verergering van die geneesmiddel se bekende farmakologiese effekte, m.a.w. slaperigheid, sedasie, tagikardie, hipotensie en anticholinergiese effekte.

Oordosering kan lei tot QT-verlenging, stuipe, status epilepticus, rabdomiolise, respiratoriese depressie, urinêre retensie, verwarring, delirium en/of agitasie, koma en dood. Pasiënte met voorafgaande ernstige kardiovaskulêre siekte kan 'n verhoogde risiko hê vir die effekte van oordosering (sien afdeling 4.4, Ortostatiese hipotensie).

Behandeling van oordosering
Daar is geen spesifieke teenmiddel vir kwetiapien nie. In gevalle van ernstige tekens, moet die moontlikheid van meervoudige medisyne-betrokkenheid oorweeg word, en intensiewe sorgprosedures word aanbeveel, insluitend die vestiging en instandhouding van 'n patentlugweg, die versekering van voldoende oksigenering en ventilasie, en die monitering en ondersteuning van die kardiovaskulêre stelsel.
Op grond van openbare literatuur kan pasiënte met delirium en agitasie en 'n duidelike antikolinergiese sindroom behandel word met fisostigmien, 1 - 2 mg (onder deurlopende EKG-monitering). Dit word nie as standaardbehandeling aanbeveel nie, as gevolg van die moontlike negatiewe effek van fisostigmien op kardiale geleiding. Fisostigmien kan gebruik word as daar geen EKG-afwykings is nie. Moet nie fisostigmien gebruik in geval van disritmieë, enige graad van hartblok of QRS-uitbreiding nie.

Die toediening van geaktiveerde koolstof moet oorweeg word.

In gevalle van kwetiapien oordosering, moet refraktiese hipotensie behandel word met toepaslike maatreëls soos binneaarse vloeistowwe en/of simpatomimetiese medisyne. Epinefrien (adrenalien) en dopamien moet vermy word, aangesien beta-stimulasie die hipotensie in die stelling van kwetiapien-geïnduseerde alfa-blokkade kan vererger.
Die noukeurige mediese toesig en monitering moet voortgesit word totdat die pasiënt herstel het.

5. FARMAKOLOGIESE EIENSKAPPE

5.1 Farmakodinamiese eienskappe

Kategorie en klas: A 2.6.5 Depressante van sentrale senuweestelsel: Diverse strukture.
Farmakoterapeutiese groep: Diasepiene, oksasepiene en tiasepiene is nog nie toegeken nie.
ATC kode: N05A H04

Meganisme van werking
Kwetiapien is 'n atipiese antipsigotiese medisyne. Kwetiapien en die aktiewe menslike plasma metaboliet, norkwetiapien interreageer met 'n wye reeks neurotransmitter-reseptore. Kwetiapien en norkwetiapien vertoon affiniteit vir breinserotonien (5HT2)- en dopamien D[1]- en D[2]- reseptore. Dit is hierdie kombinasie van reseptorantagonisme met 'n hoër selektiwiteit vir 5HT[2] relatief tot D[2]-reseptore, wat vermoedelik bydra tot die kliniese antipsigotiese eienskappe en 'n lae ekstrapiramidale newe-effek (EPN) aanspreeklikheid van kwetiapien (soos in TORQUIT) in vergelyking met tipiese antipsigotika. Kwetiapien en norkwetiapien het geen noemenswaardige affiniteit vir bensodiasepienreseptore nie, maar 'n hoë affiniteit vir histaminergiese en adrenergiese alfa1-reseptore en matige affiniteit vir adrenergiese alfa2-reseptore. Kwetiapien het ook 'n lae of geen affiniteit vir muskariniese reseptore nie, terwyl norkwetiapien matige tot hoë affiniteit by verskillende muskariniese reseptore het, wat moontlik die antikolinergiese (muskariene) effekte kan verklaar. Inhibering van NET en gedeeltelike agonistiese werking op 5HT1A-terreine deur norkwetiapien kan bydra tot die kwetiapien se terapeutiese effektiwiteit as antidepressant.

Farmakodinamiese effekte
Kwetiapien is aktief in toetse vir antipsigotiese aktiwiteit, soos gekondisioneerde vermyding. Dit blokkeer ook die werking van dopamienagoniste, gemeet hetsy gedragsmatig of elektrofisiologies, en verhoog die konsentrasies van dopamienmetaboliet, 'n neurochemiese indeks van D[2]-reseptorblokkade.
In pre-kliniese toetse wat die EPN voorspel, is kwetiapien anders as tipiese antipsigotika en het dit 'n atipiese profiel. Kwetiapien produseer nie dopamien D[2]-reseptorsupersensitiwiteit na chroniese toediening nie. Kwetiapien lewer slegs swak katalepsie by effektiewe dopamien D[2]-reseptorblokkeringsdosisse. Kwetiapien demonstreer selektiwiteit vir die limbiese stelsel deur depolarisasieblokkade te veroorsaak van die mesolimbiese, maar nie die nigrostriatale dopamienbevattende neurone na chroniese toediening nie. Kwetiapien toon minimale distoniese aanspreeklikheid aan by haloperidol-gesensitiseerde of medisyne-naïewe Cebus-ape na akute en kroniese toediening (sien afdeling 4.8).

5.2 Farmakokinetiese eienskappe

Absorpsie
Kwetiapien word goed geabsorbeer en omvattend gemetaboliseer na orale toediening. Die biobeskikbaarheid van kwetiapien word nie beduidend beïnvloed deur toediening saam met voedsel nie. Gelykvlak piek molêre konsentrasies van die aktiewe metaboliet norkwetiapien is 35 % van dit wat by kwetiapien waargeneem word.
Die farmakokinetika van kwetiapien en norkwetiapien is lineêr oor die goedgekeurde doseringsgebied.

Verspreiding
Kwetiapien is ongeveer 65 % - 83 % gebind aan plasmaproteïene.

Biotransformasie
Kwetiapien word breedvoerig deur die lewer gemetaboliseer, met ouerverbinding wat minder as 5 % van onveranderde medisyneverwante materiaal in die urine of ontlasting uitmaak, na toediening van radio-gemerkte kwetiapien. In vitro-ondersoeke het vasgestel dat CYP3A4 die primêre ensiem is wat verantwoordelik is vir sitochroom P450-gemedieerde metabolisme van kwetiapien.
Norkwetiapien is hoofsaaklik gevorm en geëlimineer deur CYP3A4.

Ongeveer 73 % van die radioaktiwiteit is uitgeskei in die urine en 21 % in die feses.

Kwetiapien en verskeie van sy metaboliete (insluitend norkwetiapien) is gevind om swak inhibeerders te wees van die menslike sitochroom P450 1A2, 2C9, 2C19, 2D6 en 3A4 aktiwiteite in vitro. In vitro CYP-inhibering word slegs waargeneem by konsentrasies ongeveer 5 tot 50-voudig hoër as wat waargeneem is in 'n dosisreeks van 300 tot 800 mg/dag by mense. Op grond van hierdie in vitro-resultate is dit onwaarskynlik dat die toediening van kwetiapien en ander medisyne kliniese beduidende medisyne-inhibisie van sitochroom P450-gemedieerde metabolisme van die ander medisyne tot gevolg sal hê. Vanuit dierestudies blyk dit dat kwetiapien sitochroom P450-ensieme kan induseer. In 'n spesifieke interaksiestudie by psigotiese pasiënte, is daar egter geen toename in die sitochroom P450-aktiwiteit gevind na toediening van kwetiapien nie.

Eliminasie
Die eliminasiehalfleeftyd van kwetiapien en norkwetiapien is onderskeidelik ongeveer 7 en 12 uur. Die gemiddelde molêre dosisfraksie van vrye kwetiapien en die aktiewe menslike plasma metaboliet norkwetiapien word < 5 % in die urine uitgeskei.

Spesiale populasies
Geslag
Die kinetika van kwetiapien verskil nie tussen mans en vroue nie.

Bejaardes
Die gemiddelde opruiming van kwetiapien by bejaardes is ongeveer 30 tot 50 % laer as by volwassenes tussen 18 en 65 jaar.

Renale inkorting
Die gemiddelde plasmaopruiming van kwetiapien is met ongeveer 25 % verminder by persone met ernstige renale inkorting (kreatinienopruiming minder as 30 ml/min/1,73m2), maar die individuele opruimingswaardes is binne die bestek van normale proefpersone.

Hepatiese inkorting
Die gemiddelde kwetiapienplasmaopruiming neem af met ongeveer 25 % by persone met bekende hepatiese inkorting (stabiele alkoholsirrose). Aangesien kwetiapien ekstensief deur die lewer gemetaboliseer word, word verhoogde plasmavlakke verwag in die populasie met hepatiese inkorting. Dosisaanpassings mag by hierdie pasiënte noodsaaklik wees (sien afdeling 4.2).

6 FARMSEUTIESE BESONDERHEDE

6.1 Lys van hulpstowwe

Kalsiumwaterstoffosfaatdihidraat
Kolloïdale anhidriese silika
Laktose monohidraat
Magnesiumstearaat
Mikrokristallien sellulose
Povidoon (K-30)
Natriumstyselglikolaat (Tipe-A)

Deklaag samestelling:
TORQUIT 25
Ferrisoksied Rooi (E172)
Ferrisoksied Geel (E172)
Hipromellose 2910 (6cps)
Makrogol 400
Titanium Dioksied (E171)

TORQUIT 100
Hipromellose 2910 (6cps)
Makrogol 400
Titanium Dioksied (E171)

TORQUIT 200
Hipromellose 2910 (6cps)
Makrogol 400
Titanium Dioksied (E171)

TORQUIT 300
Hipromellose 2910 (6cps)
Makrogol 400
Titanium Dioksied (E171)

6.2 Onverenigbaarheid

Nie van toepassing.

6.3 Rakleeftyd

5 jaar.
Stoor teen of benede 25 °C.

6.4 Spesiale voorsorgmaatreëls tydens berging

Geen spesiale voorsorgmaatreëls vir berging benodig nie.

6.5 Aard en inhoud van die houer

Stolpverpakking met wit, opaak PVC film (0,25 mm) verseël met gedrukte aluminium dekselfoelie (dikte 0,025 mm) met hitte seëllak (PVC/PVAC kopolimeer en polimetakrielaat). Elke stolpverpakking strokie bevat 10 tablette. Die stolpverpakking strokies sal in 'n buitekarton verpak word.

Nie alle verpakkingsgroottes mag moontlik bemark word nie.

6.6 Spesiale voorsorgmaatreëls vir wegdoening van gebruikte medisyne of afvalstowwe afkomstig van sulke medisyne en ander hantering van die produk

Enige ongebruikte produk moet weggedoen word volgens plaaslike vereistes.
Geen spesiale vereistes.

7. HOUER VAN REGISTRASIESERTIFIKAAT

TRINITY PHARMA (PTY) LTD
106, 16th Weg,
Midrand,
1686,
Suid Afrika.

8. REGISTRASIENOMMER(S)

TORQUIT 25: 46/2.6.5/0804
TORQUIT 100: 46/2.6.5/0805
TORQUIT 200: 46/2.6.5/0806
TORQUIT 300: 46/2.6.5/0807

9. DATUM VAN EERSTE MAGTIGING / HERNUWING VAN DIE MAGTIGING

31 Augustus 2021

10. DATUM VAN HERSIENING VAN DIE TEKS

N.A

TRINITY PHARMA