Professional Information – Proposed Clean

SCHEDULING STATUS S5

1 NAME OF THE MEDICINE

Psyquet® 100 (film-coated tablets)

Psyquet® 200 (film-coated tablets)

Psyquet® 300 (film-coated tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PSYQUET 100 tablet contains quetiapine hemifumarate equivalent to 100 mg of quetiapine.

Each PSYQUET 200 tablet contains quetiapine hemifumarate equivalent to 200 mg of quetiapine.

Each PSYQUET 300 tablet contains quetiapine hemifumarate equivalent to 300 mg of quetiapine.

Each PSYQUET 100 mg film-coated tablet contains sugar (22,82 mg lactose monohydrate).

Each PSYQUET 200 mg film-coated tablet contains sugar (45,72 mg lactose monohydrate).

Each PSYQUET 300 mg film-coated tablet contains sugar (68,58 mg lactose monohydrate).

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablets.

Psyquet 100

A yellow, round film-coated tablet with one sided breaking notch for tablet quarters.

Diameter: 8,8 mm ± 0,3 mm.

Psyquet 200

A white, round film-coated tablet with one sided breaking notch for tablet quarters.

Diameter: 11,5 mm ± 0,3 mm.

Psyquet 300

A white, oval film-coated tablet with a score line for tablet halves on both sides.

Length: 18,0 mm ± 0,3 mm.

Width: 8,8 mm ± 0,3 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

PSYQUET is indicated for the treatment of schizophrenia.

PSYQUET is also indicated for the treatment of manic episodes associated with bipolar disorder.

Safety and efficacy beyond 12 weeks have not been demonstrated.

4.2 Posology and method of administration

PSYQUET should be administered orally twice daily, with or without food.

Adults

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 to 450 mg/day. However, this may be adjusted, depending on the clinical response and tolerability of the individual patient, within the range of 150 to 750 mg/day.

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 per day by Day 6 should be in increments of no greater than 200 mg per day.

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

Elderly

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

Paediatric population

Quetiapine 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 (see section 4.3).

Renal and hepatic impairment

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

PSYQUET is contraindicated in patients with severe liver and renal impairment (see section 4.3).

4.3 Contraindications

PSYQUET is contraindicated in the following:

- Patients who are hypersensitive to any component of this product (see section 6.1).
- Pregnancy and lactation (see section 4.6).
- Children and adolescents under the age of 18 years. Safety has not been demonstrated (see section 4.4).

- Patients with severe liver and renal function impairment. Safety has not been demonstrated.
- Elderly patients with dementia exhibiting behavioural disturbances (see section 4.4).
- Co-administration with cytochrome P450 inhibitors, such as HIV-protease inhibitors, azole antifungal agents, erythromycin, and clarithromycin, is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

Paediatric population

PSYQUET 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, as in PSYQUET, 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, as in PSYQUET, 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, as in PSYQUET, 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).

Suicide/suicidal thoughts or clinical worsening

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

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

Other psychiatric conditions for which PSYQUET 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. A meta-analysis of placebo controlled clinical trials of antidepressant medicines in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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 in PSYQUET, as compared to those treated with placebo (3,0 % vs. 0 %, respectively). A population-based retrospective study of quetiapine, as in

PSYQUET, 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.

Extrapyramidal symptoms

In placebo-controlled clinical trials of adult patients quetiapine, as in PSYQUET, 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, as in PSYQUET, 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.

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, as in PSYQUET, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when PSYQUET is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine, as in PSYQUET, should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. PSYQUET 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.

QT prolongation

QT prolongation has been reported with PSYQUET. Caution must be exercised when PSYQUET is prescribed in patients with cardiovascular disease or a family history of QT prolongation (see section 4.5).

PSYQUET should be used with caution in patients who receive other hypotensive medicines or medicines that prolong the QT interval (see section 4.5).

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 PSYQUET.

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

Orthostatic hypotension

Orthostatic hypotension may occur and is more common in elderly patients than in younger patients, in particular during the initial dose-titration period.

Caution should be exercised when PSYQUET is prescribed to patients with known cardiovascular, cerebrovascular or any other disorders predisposing hypotension particularly in the elderly (these disorders and orthostatic hypotension may be exacerbated).

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience (see section 4.8). In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.

Tardive Dyskinesia

In the event of signs and symptoms of tardive dyskinesia appearing, the discontinuation of PSYQUET should be considered.

Somnolence and dizziness

Quetiapine treatment, as with PSYQUET, has been associated with somnolence and related symptoms, such as sedation, 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.

Seizures

In controlled clinical trials, there was no difference in the incidence of seizures in patients treated with quetiapine, as in PSYQUET, or placebo. No data is available about the incidence 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

PSYQUET treatment should be discontinued, and appropriate medical treatment given in patients showing the symptoms of neuroleptic malignant syndrome. Clinical manifestations of neuroleptic malignant syndrome include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase.

Severe neutropenia and agranulocytosis

Severe neutropenia (neutrophil count < 0,5 x 10^9/l) has been reported in quetiapine, as in PSYQUET, clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine, as in PSYQUET. 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. However, some cases occurred in patients without pre-existing risk factors. Quetiapine, as in PSYQUET, should be discontinued in patients with a neutrophil count < 1,0 x 10^9/l. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 x 10^9/l).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

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

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis(TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) which can be life-threatening or fatal have been reported very rarely with quetiapine treatment.
SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruriticor associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Most of these reactions occurred within 4 weeks after initiation of quetiapine therapy, some DRESS reactions occurred within 6 weeks after initiation of quetiapine therapy. If signs

and symptoms suggestive of these severe skin reactions appear, quetiapine should be withdrawn immediately, and alternative treatment should be considered.

Gradual withdrawal

Gradual withdrawal of PSYQUET is recommended because of the risk of acute withdrawal symptoms, including nausea, insomnia, headache, diarrhoea, vomiting, dizziness and irritability with abrupt cessation. Rebound psychoses may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia, and dyskinesia) has been reported. Gradual withdrawal over a period of at least one to two weeks is advisable.

Misuse and abuse

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

Sleep apnoea syndrome Sleep apnoea syndrome has been reported in patients using quetiapine, as in PSYQUET. 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, PSYQUET should be used with caution.

Interactions

See also section 4.5.

Concomitant use of PSYQUET with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases PSYQUET plasma concentrations, which could affect the efficacy of PSYQUET therapy. In patients receiving a hepatic enzyme inducer, initiation of PSYQUET treatment should only occur if the doctor considers that the benefits of PSYQUET 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 PSYQUET and should be monitored and managed as clinically appropriate in accordance with utilised antipsychotic guidelines (see section 4.8).

Hyperglycaemia

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (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 treated with any antipsychotic medicine including quetiapine, as in PSYQUET, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids

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

Elderly patients with dementia-related psychosis

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

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. PSYQUET should be used with caution in patients with risk factors for stroke.

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, as in PSYQUET, for the treatment of patients with MDD (major depressive disorder), 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 PSYQUET. PSYQUET 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, as in PSYQUET (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medicines that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with PSYQUET, 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 (see section 4.8), gallstones, and alcohol consumption.

Additional information

Quetiapine, as in PSYQUET, 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). The data showed an additive effect at week 3.

Lactose

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

PSYQUET contains lactose monohydrate, which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

The central nervous system effects of other centrally acting medicines and alcohol may be enhanced by PSYQUET and should be used with caution. The antihypertensive effects of antihypertensive medicines may be enhanced by concomitant use with PSYQUET (see section 4.4). PSYQUET should be used with caution in patients who receive other medicines that prolong the QT interval (see section 4.4).

PSYQUET may antagonise the actions of dopaminergics such as levodopa.

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

PSYQUET should not be used with potent inhibitors of the cytochrome P450 CYP3A4 isoenzyme, such as HIV protease inhibitors, erythromycin, fluconazole, itraconazole and ketoconazole, because the major route of metabolism of quetiapine involves the CYP3A4 isoenzyme and plasma concentrations of quetiapine, as in PSYQUET, can be significantly increased and co-administration is contraindicated (see section 4.3).

The pharmacokinetics of quetiapine, as PSYQUET, was not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

The pharmacokinetics of quetiapine, as PSYQUET, was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor.

PSYQUET did not alter the pharmacokinetics of lithium when used concomitantly. In a 6-week, randomised, study of lithium and extended release quetiapine versus placebo and extended release quetiapine in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group.

PSYQUET should be used with caution with inducers of the hepatic cytochrome P450 enzymes, such as carbamazepine, phenytoin, barbiturates and rifampicin as the metabolism of quetiapine, as in PSYQUET, will be increased and lower plasma concentrations can occur. This may require an adjustment to a higher dose of PSYQUET depending on the clinical response. Withdrawing hepatic enzyme inducers such as carbamazepine or phenytoin, or replacing them with non-inducer medicines (e.g. sodium valproate) may require a reduced dose adjustment of PSYQUET.

The pharmacokinetics of sodium valproate and PSYQUET were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, as in PSYQUET, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

The pharmacokinetics of quetiapine, as in PSYQUET, was not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused increases in the clearance of quetiapine.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

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

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

4.6 Fertility, pregnancy and lactation

PSYQUET is contraindicated for use during pregnancy and lactation as safety has not been demonstrated (see section 4.3).

4.7 Effects on ability to drive and use machines

Patients should avoid operating hazardous machines, including motor vehicles, as PSYQUET may cause drowsiness or dizziness.

4.8 Undesirable effects

Blood and the lymphatic system disorders

Frequent: Decreased haemoglobin, leucopenia, decreased neutrophil count, increased eosinophils.

Less frequent: Neutropenia, thrombocytopenia, anaemia, decreased platelet count, agranulocytosis.

Immune system disorders

Less frequent: Hypersensitivity (including allergic skin reactions like angioedema, anaphylaxis, urticaria/rash), Stevens-Johnson syndrome (SJS), anaphylactic reaction.

Endocrine disorders

***Frequent*:** Hyperprolactinaemia, decreases in total T_4, decreases in free T_4, decreases in total T_3, increases in TSH.

Less frequent: Decrease in free T_3, hypothyroidism, inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Frequent: Elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, increased appetite, blood glucose increased to hyperglycaemic levels.

Less frequent: Hyponatraemia, diabetes mellitus, exacerbation of pre-existing diabetes, metabolic syndrome.

Psychiatric disorders

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

***Less frequent*:** Somnambulism and related reactions such as sleep talking and sleep related eating disorder.

Nervous system disorders

Frequent: Headache, somnolence, dizziness, extrapyramidal symptoms, anxiety, and dysarthria.

Less frequent: Seizures, restless legs syndrome, tardive dyskinesia, syncope.

Eye disorders

Less frequent: Dry eyes, blurred vision, asymptomatic changes in the lens of the eye with long-term treatment.

Ear and labyrinth disorders

Less frequent: Ear pain.

Cardiac disorders

***Frequen*t:** Tachycardia, palpitations.

***Less frequen*t:** QT prolongation, bradycardia.

Frequency not known: Cardiomyopathy and myocarditis

Vascular disorders

Frequent: Orthostatic hypotension.

Less frequent: Venous thromboembolism, stroke.

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea.

Less frequent: Rhinitis.

Gastrointestinal disorders

Frequent: Dyspepsia, dry mouth, constipation, vomiting.

Less frequent: Dysphagia, pancreatitis, intestinal obstruction / ileus.

Hepato-biliary disorders

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

Less frequent: Elevations in serum aspartate aminotransferase (AST), jaundice, hepatitis.

Skin and subcutaneous tissue disorders

Less frequent: Angioedema, Stevens-Johnson syndrome (SJS).

Frequency not known: Toxic epidermal necrolysis, erythema multiforme, Acute Generalised Exanthematous Pustulosis (AGEP) medicine rash with eosinophilia and systemic symptoms (DRESS), cutaneous vasculitis.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Rhabdomyolysis.

Renal and urinary disorders

Less frequent: Urinary tract infection.

Pregnancy, puerperium and perinatal conditions

Frequency not known: Medicines withdrawal symptoms in neonates.

Reproductive system and breast disorders

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

General disorders

Frequent: Withdrawal (discontinuation) symptoms, mild asthenia, peripheral oedema, irritability, pyrexia.

Less frequent: Neuroleptic malignant syndrome, hypothermia.

Investigations

Less frequent*:* Elevation in blood creatinine phosphokinase.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8
Suspected adverse reactions can also be reported directly to the HCR via Patientsafety.sacg@novartis.com.

4.9 Overdose

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects.
Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. 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, as in PSYQUET. In cases of severe signs, the possibility of multiple medicine 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.

Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible, to perform within one hour of ingestion. The administration of activated charcoal should be considered.

In cases of quetiapine, as in PSYQUET, overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic medicines. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines

ATC code: N05A H04

Pharmacological Classification: A 2.6.5 Central nervous system depressants: Miscellaneous structures

Mechanism of action

Quetiapine is a dibenzothiazepine atypical antipsychotic agent and interacts with various neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin receptors (5-HT_2) in the brain than it does for dopamine D_1 and D_2 receptors in the brain. It also has high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic alpha-2 receptors. Quetiapine has no significant affinity for cholinergic, muscarinic or benzodiazepine receptors. Quetiapine does not produce sustained elevation in prolactin in man. Quetiapine occupies the $5HT_2$ and D_2 receptors for up to 12 hours after dosing when given twice daily.

Quetiapine and several of its metabolites were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities, but only at concentrations at least 10 to 50-fold higher than those observed in the usual effective dose range of 300 to 450 mg/day in humans.

5.2 Pharmacokinetic properties

Quetiapine is well absorbed after oral doses, widely distributed throughout the body and is about 83 % bound to plasma proteins. Quetiapine reaches peak plasma levels after 1,5 hours. The bioavailability of quetiapine is not significantly affected by administration with food. Quetiapine is extensively metabolised following oral administration by hepatic cytochrome P450, CYP3A4 isoenzyme and oxidation to inactive and readily excreted sulfoxide and acidic derivatives. It is excreted mainly via the urine (73 %) and about 20 % in the faeces. The elimination half-life of quetiapine is approximately 6 to 7 hours.

The pharmacokinetics of quetiapine is similar in both genders.

The mean clearance of quetiapine in the elderly is approximately 30 % to 50 % less than in adults aged 18 to 65 years.

In patients with severe renal impairment (creatinine clearance less than 30 ml/min/1,73 m^2) and in patients with hepatic impairment (stable alcoholic cirrhosis), the mean plasma clearance of quetiapine is reduced by about 25 %, but the individual clearance values are within the range for normal patients (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Calcium hydrogen phosphate dehydrate, cellulose microcrystalline, lactose monohydrate, magnesium stearate, povidone, silica colloidal hydrated, sodium starch glycollate (type A).

Coating

*Opadry II white, iron oxide yellow (only for the 100 mg tablet).

*Opadry II white consists of: hypromellose, lactose monohydrate, macrogol 4000, titanium dioxide (E 171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

48 months.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Psyquet 100 tablets are packed as 90 tablets in either

- Clear, transparent PVC/COC/PVDC/aluminium blisters or PVC/PE/PVDC/aluminium blisters in cartons. Each carton contains 9 blisters with 10 tablets per blister, or
- White HDPE securitainers.

Psyquet 200 tablets are packed as 60 tablets in either

- Clear, transparent PVC/COC/PVDC/aluminium blisters or PVC/PE/PVDC/aluminium blisters in cartons. Each carton contains 6 blisters with 10 tablets per blister, or

- White HDPE securitainers.

Psyquet 300 tablets are packed as 60 tablets in either:

- Clear, transparent PVC/COC/PVDC/aluminium blisters or PVC/PE/PVDC/aluminium blisters in cartons. Each carton contains 6 blisters with 10 tablets per blister, or
- White HDPE securitainers.

Not all packs may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

No special requirement for disposal.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Magwa Crescent West

Waterfall City

Jukskei View

Midrand

2090

8 REGISTRATION NUMBERS

Psyquet 100: 43/2.6.5/0849

Psyquet 200: 43/2.6.5/0850

Psyquet 300: 43/2.6.5/0851

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2012

10 DATE OF REVISION OF THE TEXT

02 November 2021

[1]Company Reg. No.: 1990/001979/07