CLEAN PROPOSED PROFESSSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

AROQUET 25/100/200/300 (film coated tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AROQUET 25 (film-coated tablet): Each film coated tablet contains quetiapine fumarate 28,78 mg equivalent to 25 mg of quetiapine.

AROQUET 100 (film-coated tablet): Each film coated tablet contains quetiapine fumarate 115,12 mg equivalent to 100 mg of quetiapine.

AROQUET 200 (film-coated tablet): Each film coated tablet contains quetiapine fumarate 230,24 mg equivalent to 200 mg of quetiapine.

AROQUET 300 (film-coated tablet): Each film coated tablet contains quetiapine fumarate 345,36 mg equivalent to 300 mg of quetiapine.

Excipient(s) with known effects: Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

AROQUET 25 (film-coated tablet)**:** Pink coloured, round shaped, biconvex, film coated tablets, plain on both sides.

AROQUET 100 (film-coated tablet): Yellow coloured, round shaped, biconvex, film coated tablets, plain on both sides.

AROQUET 200 (film-coated tablet): White to off white, round shaped, biconvex, film coated

tablets, plain on both sides.

AROQUET 300 (film-coated tablet)**:** White to off white, capsule shaped, biconvex, film coated tablets, debossed with “300” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AROQUET is indicated for the treatment of schizophrenia.

AROQUET 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

Adults

For the treatment of schizophrenia, the total daily dose for the first 4 days of therapy is 50 mg (Day 1; 25 mg twice daily), 100 mg (Day 2; 50 mg twice daily), 200 mg (Day 3; 100 mg twice daily) and 300 mg (Day 4; 150 mg twice daily).

From Day 4 onwards, the dose should be titrated to the effective dose range of 300 to 450 mg/day although the daily dose may be adjusted in some patients within the range 150 to 750 mg/day, depending on the clinical response and tolerability of the individual patient.

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; 50 mg twice daily), 200 mg (Day 2; 100 mg twice daily), 300 mg (Day 3; 150 mg twice daily) and 400 mg (Day 4; 200 mg twice daily). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

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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

AROQUET treatment should be given with caution in the elderly with reduced initial and target dosages, and slower dosage titrations that may be required in these patients. Elderly patients should be started on quetiapine 25 mg/day. The dose should be increased daily, in increments of 25 to 50 mg, to an effective dose.

Renal and hepatic impairment

AROQUET should be given with caution and in reduced doses to patients with hepatic and renal impairment as clearance of quetiapine is reduced by approximately 25 % in these patients.

A starting dose of 25 mg/day **AROQUET** is recommended to be increased daily in increments of 25 to 50 mg to an effective dose.

Method of administration

AROQUET should be administered orally twice daily as 2 divided doses, with or without food.

4.3 Contraindications

AROQUET is contraindicated in the following:

- Hypersensitivity to quetiapine or to any of the inactive ingredients in **AROQUET** (see

section 6.1).

- Pregnancy and lactation as safety has not been demonstrated (see section 4.6).
- Safety in children and adolescents has not been demonstrated.
- Patients with advanced liver and renal function impairment.
- Concomitant administration of cytochrome P450 3A4 inhibitors such as HIV-protease inhibitors, azole-antifungal medicines, erythromycin, clarithromycin and nefazodone (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.

Other psychiatric conditions for which **AROQUET** 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.

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Close supervision of patients and in particular those at high risk should accompany drug 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.

Severe neutropenia and agranulocytosis

Severe neutropenia (neutrophil count < 0.5 x 10^9/L) has been reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of 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 drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count < 1.0 x 10^9/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x 10^9/L) (see section 5.1).

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 therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

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Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some extreme cases associated with ketoacidosis or hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics, including **AROQUET.**

Patients with an established diabetes mellitus who are on atypical antipsychotics such as **AROQUET**, should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics such as **AROQUET**, should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics such as **AROQUET**, should undergo fasting blood glucose testing. Hyperglycaemia was resolved in some patients upon discontinuation of atypical antipsychotics such as **AROQUET**. However, some patients still required the continuation of antidiabetic treatment despite the cessation of the suspect medicine.

Cardiovascular disease

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 **AROQUET** 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).

Precaution should be exercised especially in the elderly when **AROQUET** is prescribed concomitantly with medicines known to prolong the QTc interval.

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Tardive Dyskinesia and Extrapyramidal Symptoms (EPS)

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

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.

Seizures

Patients with a history of seizures should be treated with caution.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome has been associated with quetiapine as contained in **AROQUET** treatment. Clinical manifestations of neuroleptic malignant syndrome include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. **AROQUET** treatment should be discontinued and appropriate medical treatment given.

Lipids

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

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).

Pancreatitis

Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see section 4.4), gallstones, and alcohol consumption.

Concomitant illnesses

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

QT prolongation

In clinical trials, 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 quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine 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).

Dysphagia

Dysphagia (see section 4.8) has been reported with quetiapine. **AROQUET** 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 often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with **AROQUET** and preventive measures undertaken.

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, however, a causal relationship to quetiapine has not been established. Treatment with **AROQUET** 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).

Misuse and abuse

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

Elderly patients with dementia-related psychosis

Quetiapine as in **AROQUET** 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. **AROQUET** 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.

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.

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptors subtype. 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.

AROQUET should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. **AROQUET** should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see sections 4.5, 4.8, 5.1 and 4.9).

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 sections 4.8 and 5.1).

Somnolence and dizziness

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8).

In clinical trials for treatment of patients with bipolar depression, 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.

AROQUET 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, **AROQUET** should be used with caution.

Interactions

See section 4.5.

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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 **AROQUET** therapy. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

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 5.1). The data showed an additive effect at week 3.

Lactose

AROQUET contains lactose, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take **AROQUET.**

4.5 Interaction with other medicinal products and other forms of interaction

The central nervous system effects of other centrally acting medicines and alcohol may be enhanced by **AROQUET** and should be used with caution.

The antihypertensive effects of antihypertensive medicines may be enhanced by concomitant used with **AROQUET**.

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, including erythromycin and fluconazole is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

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 quetiapine treatment should only occur if the physician 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). This may require a reduced dose adjustment of **AROQUET**.

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

Quetiapine did not alter the pharmacokinetics of lithium when used concomitantly.

AROQUET 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 will be increased. This may require an adjustment of the **AROQUET** dosage depending of the clinical response.

The pharmacokinetics of quetiapine was not significantly altered following co-administration with the antipsychotic's risperidone or haloperidol.

Concomitant use of quetiapine and thioridazine caused increases in the oral clearance of quetiapine.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation

AROQUET is contraindicated 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, because **AROQUET** may cause somnolence.

4.8 Undesirable effects

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.

Table 1: Undesirable effects as per System Organ Class

SYSTEM ORGAN CLASS	INCIDENCE	ADVERSE REACTION
Blood and lymphatic system disorders	Frequent	Decreased haemoglobin[22], leucopenia[1, 28], decreased neutrophil count, eosinophils increased[27]
	Less frequent	Neutropenia[1], thrombocytopenia, anaemia, platelet count decreased[13], agranulocytosis[26]
Immune system disorders	Less frequent	Hypersensitivity (including allergic skin reactions), anaphylactic reaction[5]
Endocrine disorders	Frequent	Hyperprolactinaemia[15], decreases in total T4[24], decreases in free T4[24],

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		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	Elevations in serum triglyceride levels[10,30], elevations in total cholesterol (predominantly LDL cholesterol)[11,30], decreases in HDL cholesterol[17,30], weight gain[8,30], increased appetite, blood glucose increased to hyperglycaemic levels[6, 30]
	Less frequent	Hyponatraemia[19], diabetes mellitus[1,5], exacerbation of pre-existing diabetes, metabolic syndrome[29]
Psychiatric disorders	Frequent	Abnormal dreams and nightmares, suicidal

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		ideation and suicidal behaviour[20]
	Less frequent	Somnambulism and related reactions such as sleep talking and sleep related eating disorder
Nervous system disorders	Frequent	Dizziness[4,16], somnolence[2,16], headache, extrapyramidal symptoms[1,21], dysarthria
	Less frequent	Seizure[1], restless legs syndrome, tardive dyskinesia[1,5], syncope[4,16]
Cardiac disorders	Frequent	Tachycardia[4], palpitations[23]
	Less frequent	QT prolongation[1,12,18], bradycardia[32]
Eye disorders	Frequent	Vision blurred
Vascular disorders	Frequent	Orthostatic hypotension[4,16]
	Less frequent	Venous thromboembolism[1]
	Frequency unknown	Stroke[33]
	Frequent	Dyspnoea[23]

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Respiratory, thoracic and mediastinal disorders	Less frequent	Rhinitis
Gastro-intestinal disorders	Frequent	Dry mouth, constipation, dyspepsia, vomiting[25]
	Less frequent	Dysphagia[7], pancreatitis[1], intestinal obstruction/Ileus
Hepato-biliary disorders	Frequent	Elevations in serum alanine aminotransferase (ALT)[3], elevations in gamma-GT levels[3]
	Less frequent	Elevations in serum aspartate aminotransferase (AST)[3], jaundice[5], hepatitis
Skin and subcutaneous tissue disorders	Less frequent	Angioedema[5], Stevens-Johnson syndrome[5]
	Frequency unknown	Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Rash with Eosinophilia And Systemic Symptoms (DRESS)

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Musculo-skeletal and connective tissue disorders	Less frequent	Rhabdomyolysis
Renal and urinary disorders	Less frequent	Urinary retention
Pregnancy, puerperium and perinatal conditions	Frequency unknown	Drug withdrawal syndrome neonatal[31]
Reproductive system and breast disorders	Less frequent	Sexual dysfunction, priapism, galactorrhoea, breast swelling, menstrual disorder
General disorders and administration site conditions	Frequent	Withdrawal (discontinuation) symptoms[1,9], mild asthenia, peripheral oedema, irritability, pyrexia
	Less frequent	Neuroleptic malignant syndrome[1], hypothermia
Investigations	Less frequent	Elevations in blood creatine phosphokinase[14]

1. See section 4.4

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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. 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 have 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 (≥

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5.172 mmol/L) (patients < 18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).

12. See text below.

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

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

15. Prolactin levels (patients > 18 years of age): > 20 µg/L (> 869.56 pmol/L) males; >30 µg/L (> 1304.34 pmol/L) females at any time.

16. May lead to falls.

17. HDL cholesterol: < 40 mg/dL (1.025 mmol/L) males; < 50 mg/dL (1.282 mmol/L) females at any time.

18. Incidence of patients who have a QTc shift from < 450 msec to ≥ 450 msec with a ≥ 30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.

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

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

21. See section 5.1.

22. Decreased haemoglobin to ≤ 13 g/dL (8.07 mmol/L) males, ≤ 12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11 % of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was –1.50 g/dL.

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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 10^9L at baseline to < 0.5 x 10^9/L at any time during treatment and based on patients with severe neutropenia (< 0.5 x 10^9/L) and infection during all quetiapine clinical trials (see section 4.4).

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

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

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

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

31. See section 4.6

32. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.

33. Based on one retrospective non-randomised epidemiological study.

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

class effects.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Hypotension, tachycardia and somnolence are the main clinical symptoms in patients who had taken an overdose of quetiapine. There is no specific antidote to quetiapine and treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines.

ATC code: N05A H04

Category and class: A 2.6.5 Central nervous system depressants:

Miscellaneous structures

Mechanism of action

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Quetiapine is an atypical antipsychotic medicine which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin ($5HT_2$) receptors in the brain than it does for dopamine D_1 and D_2 receptors in the brain. Quetiapine also has high affinity at histaminergic and adrenergic alpha-1 receptors, with a lower affinity at adrenergic alpha-2 receptors, but no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors. In animal models, quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance.

Quetiapine does not produce sustained elevations in prolactin in man.

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

5.2 Pharmacokinetic properties

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 83 % bound to plasma proteins.

Biotransformation

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Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5 % of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine. *In vitro* investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

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 medicines. 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.

CLEAN PROPOSED PROFESSSIONAL INFORMATION

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/1.73m^2), 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

AROQUET 25/100/200/300 (film-coated tablet)

Lactose monohydrate

Sodium starch glycolate (Type A)

Dibasic calcium hydrogen phosphate dihydrate

Povidone K30

Cellulose Microcrystalline (PH102)

CLEAN PROPOSED PROFESSSIONAL INFORMATION

Magnesium stearate

Film coating

AROQUET 25: Opadry Pink

AROQUET 100: Opadry Yellow

AROQUET 200/300:

Hypromellose E-5

Macrogol 400

Titanium Dioxide

6.2 Shelf life

30 months

Store at or below 25 °C.

Protect from light and moisture.

Do not remove the tablets from the container until required for use.

KEEP ALL MEDICINES OUT OF REACH AND SIGHT OF CHILDREN.

Do not use the tablets after the expiry date printed on the container.

Return all unused medicine to your pharmacist.

Do not dispose of unused medicine in drains and sewerage systems (e.g. toilets)

6.3 Special precautions for storage

This medicine does not contain any special storage conditions.

6.4 Nature and contents of container

AROQUET 25/100/200/300 tablets are packed into clear transparent PVC / silver aluminium

blisters strips, containing 10/12/15 tablets each.

AROQUET 25: Pink coloured, round shaped, biconvex, film coated tablets, plain on both sides.

AROQUET 100: Yellow coloured, round shaped, biconvex, film coated tablets, plain on both sides.

AROQUET 200: White to off white, round shaped, biconvex, film coated tablets, plain on both sides.

AROQUET 300: White to off white, capsule shaped, biconvex, film coated tablets, debossed with “300” on one side and plain on other side.

AROQUET 25/100/200/300 tablets are packed into clear transparent / silver aluminium blisters strips, containing 10/12/15 tablets each.

AROQUET 25: Pack sizes of 100 tablets

AROQUET 100: Pack sizes of 90 tablets

AROQUET 200: Pack sizes of 60 tablets

AROQUET 300: Pack sizes of 60 tablets

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park, Building 2

6 Coombe Place

Rivonia

Johannesburg

South Africa

CLEAN PROPOSED PROFESSSIONAL INFORMATION

8. REGISTRATION NUMBER(S)

AROQUET 25: 47/2.6.5/0633

AROQUET 100: 47/2.6.5/0634

AROQUET 200: 47/2.6.5/0635

AROQUET 300: 47/2.6.5/0636

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 February 2021

10. DATE OF REVISION OF THE TEXT

To be confirmed