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PROFESSSIONAL INFORMATION LEAFLET

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

AROQUET XR 50/150/200/300/400 (prolonged-release tablet)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AROQUET XR 50 *prolonged-release tablet:*

Each prolonged-released tablet contains 50 mg quetiapine fumarate equivalent of quetiapine.

AROQUET XR 150 *XR prolonged-release tablet:*

Each prolonged-released tablet contains 150 mg quetiapine fumarate equivalent of quetiapine.

AROQUET XR 200 *XR prolonged-release tablet:*

Each prolonged-released tablet contains 200 mg quetiapine fumarate equivalent of quetiapine.

AROQUET XR 300 *XR prolonged-release tablet:*

Each prolonged-released tablet contains 300 mg quetiapine fumarate equivalent of quetiapine.

AROQUET XR 400 *XR prolonged-release tablet:*

Each prolonged-released tablet contains 400 mg quetiapine fumarate equivalent of quetiapine.

Excipient(s) with known effects: Lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

AROQUET XR 50 *prolonged-release tablet:*

Peach coloured, round shaped, biconvex film coated tablets, debossed with Q50 on one side and plain on the other.

AROQUET XR 150 *prolonged-release tablet:*

White to off white, capsule shaped, biconvex, film coated tablets, debossed with 'AB2' on one side and plain on the other side.

AROQUET XR 200 *prolonged-release tablet:*

Yellow coloured, round shaped, biconvex film coated tablets, debossed with 'I2' on one side and plain on the other.

AROQUET XR 300 *prolonged-release tablet:*

Light yellow coloured, round shaped, biconvex film coated tablets, debossed with 'Q300' on one side and plain on the other.

AROQUET XR 400 *prolonged-release tablet:*

White coloured, round shaped, biconvex, film coated tablets debossed with 'I4' on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AROQUET XR 50/150/200/300/400 is indicated for the treatment of:

- Schizophrenia
- Preventing relapse in stable schizophrenic patients who have been maintained on **AROQUET XR.**
- Bipolar disorder including:
    - Manic episodes associated with bipolar disorder
    - Depressive episodes associated with bipolar disorder

- Preventing recurrence in the maintenance treatment of bipolar disorder (manic, mixed or depressive episodes) as monotherapy or in combination with mood stabilisers

- Major depressive disorder
- Preventing relapse in stable major depressive disorder patients who have been maintained on **AROQUET XR.**

4.2 Posology and method of administration

Posology

Adults

For the treatment of schizophrenia

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400-800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For treatment of manic episodes associated with bipolar disorder

The daily dose at the start of therapy is 300 mg on Day 1, 600 mg on Day 2 and up to 800 mg after Day 2. The dose should be adjusted within the effective dose range of 400-800 mg per day, depending on the clinical response and tolerability of the patient.

For the treatment of depressive episodes associated with bipolar disorder

AROQUET XR should be administered once daily in the evening.

AROQUET XR should be titrated as follows: 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). **AROQUET XR** can be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Antidepressant efficacy was demonstrated with **AROQUET XR** at 300 mg and 600 mg, however no additional benefit was seen in the 600 mg group during short-term treatment.

For preventing recurrence in maintenance treatment of bipolar disorder

Patients who have responded to **AROQUET XR** in combination therapy to a mood stabiliser (lithium or valproate) for acute treatment of bipolar disorder should continue on **AROQUET XR** therapy at the same dose. The **AROQUET XR** dose can be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 400-800 mg/day. Patients who have responded to **AROQUET XR** for acute treatment of bipolar disorder should continue on **AROQUET XR** therapy at the same dosing regimen. **AROQUET XR** dose can be re-adjusted depending on clinical response and tolerability of the individual patients within the dose range of 300-800 mg/day.

For treatment of major depressive disorder

AROQUET XR should be administered once daily in the evening. Initial dosing should begin at 50 mg on Day 1 and 2, increased to 150 mg on Day 3 and 4. Further adjustments can be made upwards or downwards within the recommended dose range of 50-300 mg depending upon the clinical response and tolerability of the patient. For maintenance therapy in major depressive disorder the effective dose during initial treatment should be continued. The dose can be adjusted within the recommended dose range depending upon the clinical response and tolerability of the patient.

Switching from quetiapine immediate-release tablets

For more convenient dosing, patients who are currently being treated with divided doses of a quetiapine immediate release dosage form may be switched to **AROQUET XR** at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Special Populations

Elderly

AROQUET XR should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of **AROQUET XR** may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30-50 % in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in increments on 50 mg/day to an effective dose, depending on the clinical response and tolerance of the individual patient. In elderly patients with major depressive disorder initial dosing should begin at 50 mg on Days 1-3, the dose can be increased to 100 mg on Day 4, 150 mg on Day 8 and then up to 300 mg depending on clinical response and tolerability.

Renal and hepatic impairment

Renal impairment

Dosage adjustment is not necessary in patients with renal impairment

Hepatic impairment

AROQUET XR is extensively metabolised by the liver. Therefore, **AROQUET XR** should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability on the individual patient.

Paediatric Population

Children and adolescents

No data are available.

Method of administration

AROQUET XR should be administered once daily, with or without food. The tablets should be swallowed whole and not split, chewed or crushed.

4.3 Contraindications

AROQUET XR is contraindicated in patients who are hypersensitive to quetiapine or to any of the excipients of **AROQUET XR.**

- Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal medicines, erythromycin, clarithromycin and nefazodone, is contraindicated (see section 4.5).
- Pregnancy and lactation, as safety has not been demonstrated (see section 4.6).
- Children and adolescents, as safety and efficacy in children and adolescents have not been demonstrated.
- Advanced liver and renal dysfunction, as safety has not been demonstrated.

4.4 Special warnings and precautions for use

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including quetiapine. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics 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 should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect medicine.

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 XR** 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 disorder. The same precautions observed when treating patients with major depressive disorder 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.

Tardive dyskinesia and extrapyramidal symptoms

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

In placebo-controlled clinical trials for schizophrenia and bipolar mania the incidence of extrapyramidal symptoms was no different from that of placebo across the recommended therapeutic dose range. This predicts that quetiapine has less potential than typical antipsychotic medicines to induce tardive dyskinesia in schizophrenia and bipolar mania patients. In short-term, placebo-controlled clinical trials for bipolar depression and major depressive disorder the incidence of EPS was higher in quetiapine treated patients than in placebo treated patients (see section 4.8).

Severe neutropenia and agranulocytosis

Severe neutropenia (< 0,5 X 10^9/ℓ) has been uncommonly reported in **AROQUET XR** clinical trials. Most cases of severe neutropenia have occurred within the first 2 months of starting therapy with **AROQUET XR**. There was no apparent dose relationship. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of medicine induced neutropenia. **AROQUET XR** should be discontinued in patients with a neutrophil count < 1,0 X 10^9/ℓ. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1,5 X 10^9/ℓ) (see section 4.8).

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

Seizures

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

Concomitant illness

AROQUET XR should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. **AROQUET XR** may induce orthostatic hypotension especially during the initial dose-titration period.

Lipids

Increases in triglycerides and cholesterol and decreases in HDL have been observed in clinical trials with **AROQUET XR** (see section 4.8). Lipid changes should be managed as clinically appropriate.

Neuroleptic malignant syndrome

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

QT prolongation

In clinical trials quetiapine was not associated with a persistent increase in absolute QT intervals. However, in post marketing experience there were cases reported of QT prolongation with overdose. As with other antipsychotics, caution should be exercised when **AROQUET XR** is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when **AROQUET XR** is prescribed either with medicines known to increase QT interval or with concomitant neuroleptics, especially for patients with increased risk of QT prolongation, i.e. the

elderly, patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia, or hypomagnesaemia (see section 4.5).

Withdrawal

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

Elderly patients with dementia

AROQUET XR is not approved for the treatment of dementia-related psychosis. In a meta-analysis of atypical antipsychotic medicines, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo-controlled quetiapine studies in the same patient population (n = 710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5,5 % versus 3,2 % in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.

Interactions

Concomitant use of **AROQUET XR** with hepatic enzyme inducers such as carbamazepine may substantially decrease systemic exposure to quetiapine. Depending on clinical response, higher doses of **AROQUET XR** may need to be considered if used concomitantly with a hepatic enzyme inducer.

During concomitant administration of medicines, which are potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors), plasma concentrations of quetiapine can be significantly higher than observed in patients in clinical trials. As a consequence, concomitant use is contraindicated (see sections 4.3 and 4.5). Special consideration should be given in elderly and debilitated patients. The risk-benefit ratio needs to be considered on an individual basis in all patients.

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 agent including quetiapine, 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.

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 4.4), gallstones and alcohol consumption.

Dysphagia

Dysphagia (see section 4.8) has been reported with quetiapine. Quetiapine 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.

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 quetiapine should be reassessed in patients with suspected cardiomyopathy or myocarditis.

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.

Misuse and abuse

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

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. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine 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).

Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

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).

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, **AROQUET XR** 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 anticholinergic (muscarinic) effects (see section 4.3).

CYP3A4 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. The mean half-life of **AROQUET XR** increased from 2,6-6,8 hours, but the mean T_{max} was unchanged. Due to the potential for an interaction of similar magnitude in a clinical setting, concomitant use of **AROQUET XR** and potent CYP3A4 inhibitors such as azole antifungals, macrolide antibiotics, and protease inhibitors is contraindicated (see section 4.3). It is also not recommended to consume grapefruit juice while on **AROQUET XR**.

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 **AROQUET XR.**

This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13 % of the exposure during administration of **AROQUET XR** 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 **AROQUET XR**. Co-administration of **AROQUET XR** and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approximately 450 %.

In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur after the medical practitioner considered the benefit risk assessment for an individual patient. 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 4.3).

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

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotic medicines, risperidone or haloperidol. Concomitant use of **AROQUET XR** and thioridazine caused an increased clearance of quetiapine with approximately 70 %.

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 **AROQUET XR** is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

4.6 Fertility, pregnancy and lactation

Fertility

The effects of quetiapine on human fertility have not been assessed.

Pregnancy

AROQUET XR is contraindicated during pregnancy as safety and efficacy of **AROQUET XR d**uring pregnancy has not been established (see section 4.3).

Lactation

AROQUET XR is contraindicated during lactation. The degree to which quetiapine is excreted into human milk is unknown. Women who are breastfeeding should therefore be advised not to breastfeed while taking **AROQUET XR** (see section 4.3).

4.7 Effects on ability to drive and use machines

AROQUET XR may cause drowsiness, which may interfere with mental alertness. Patients are therefore advised to use this medicine with caution pertaining to driving or operating machinery.

4.8 Undesirable effects

System Organ Class	Frequency	Event
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], Angranulocytosis[26]
Immune system disorders	Less frequent	Hypersensitivity (including allergic skin reactions), Anaphylactic reaction[5]
Endocrine disorders	Frequent	Hyperprolactinaemia[15], Decreases in total T_4[24], Decreases in free T_4[24], Decreases in total T_3[24], Increases in TSH[24]

	Less frequent	Decreases in free T_3[24], Hypothyroidism[21], Inappropriate antidiuretic hormone secretion	
Metabolism and nutritional 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 ideation and suicidal behavior[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], Dysathria	
	Less frequent	Seizure[1], Restless legs syndrome, Tardive dyskinesia[1,5], Syncope[4,16]	
Cardiac disorder	Frequent	Tarchycardia[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]	
Respiratory, thoracic, and mediastinal disorders	Frequent	Dyspnoea[23]	
	Less frequent	Rhinitis	
Gastrointestinal disorders	Frequent	Dry mouth, Constipation, Dyspepsia, Vomiting[25]	
	Less frequent	Dysphagia[7], Pancreatitis[1], Intestinal obstructions/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	Less frequent	Angioedema[5], Stevens-Johnson syndrome[5]	

subcutaneous tissue disorders	Frequency unknown	Toxic Epidermal Necrolysis, Erythema Multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)	
Musculoskeletal 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	Frequent	Elevations in serum triglyceride levels[11], Elevations in total cholesterol (predominantly LDL cholesterol)[11], Decreased in HDL Cholesterol[17], Weight Gain[8], Elevations in serum transaminases (ALT, AST)[3], Decreased neutrophil count[26], Increased blood glucose to hyperglycaemic level[6] , Elevations in serum prolactin[15]
	Less frequent	Elevations in gamma-GT levels[3], Platelet count decreased[13], Elevations in blood creatine Phosphokinase[14]

(1) See section 4.4.

(2) Somnolence may occur, usually during the first 2 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 have only been taken from post-marketing data with the immediate release formulation of quetiapine.

(6) Fasting blood glucose ≥126mg/dL (≥7.0 mmol/L) or a non-fasting blood glucose ≥200mg/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 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.

(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 T_4, free T_4, total T_3 and free T_3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.

(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 10^9/L 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 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), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with quetiapine treatment.

Thyroid level:

Quetiapine 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 2-4 weeks of quetiapine treatment, with no further reduction during long-term treatment.
No significant clinical evidence exists for changes is TSH concentration over time. Nearly all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total 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 causes clinically relevant hypothyroidism.

Extrapyramidal symptoms:

The following clinical trials (monotherapy and combination therapy) included treatment with quetiapine and **AROQUET XR**: In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7,8 % for quetiapine and 8,0 % for placebo; bipolar mania: 11,2 % for quetiapine and 11,4 % for placebo). In short-term, placebo-controlled clinical trials in bipolar depression the aggregated incidence of extrapyramidal symptoms was 8,9 % for quetiapine compared to 3,8 % for placebo, though the incidence of the individual adverse events (e.g. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4 % in any treatment group. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5,4 % for **AROQUET XR** and 3,2 % for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9,0 % for **AROQUET XR** and 2,3 % for placebo. In long-term studies of schizophrenia, bipolar disorder and major depressive disorder the aggregated exposure adjusted incidence of treatment-emergent extrapyramidal symptoms was similar between quetiapine and placebo.

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 Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of 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 4.3, Orthostatic hypotension).

Management of overdose

There is no specific antidote to **AROQUET XR**. In cases of severe signs, the possibility of multiple drug 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.

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, Category and class: A 2.6.5: Central nervous system depressants: Miscellaneous structures

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 ($5HT_2$) and dopamine D_1 and D_2 receptors. It is this

combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to dopamine D_2 receptors which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of quetiapine. Additionally, norquetiapine has high affinity for the norepinephrine transporter (NET). Quetiapine and norquetiapine also have high affinity at histaminergic and adrenergic alpha1 receptors, with a lower affinity at adrenergic alpha2 and serotonin $5HT_1A$ receptors. Quetiapine has no appreciable affinity at cholinergic muscarinic or benzodiazepine receptors.

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

It also reverses 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 super-sensitivity 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 A10 mesolimbic but not the A9 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.

5.2 Pharmacokinetic properties

Absorption and distribution

Quetiapine is absorbed and extensively metabolised following oral administration.

Quetiapine is approximately 83 % bound to plasma proteins. 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 and dose-proportional for doses up to 800 mg administered once daily. The kinetics of quetiapine does not differ between men and women.

Quetiapine achieves peak plasma concentrations at approximately 6 hours after administration (T_{max}).

Quetiapine displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. The maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) for quetiapine administered once daily are comparable to those achieved for the same total daily dose of immediate release quetiapine fumarate administered twice daily.

When quetiapine prolonged released administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate administered twice daily, the area under the quetiapine plasma concentration-time curve (AUC) is equivalent; but the maximum plasma (C_{max}) is 13 % lower. When quetiapine prolonged released administered once daily is compared to the same total daily dose of the immediate release formulation of quetiapine administered once daily, the quetiapine prolonged released AUC is equivalent; and C_{max} is 59 % lower. The AUC and C_{max} for the metabolite norquetiapine are 37 % and 18 % lower than the immediate-release quetiapine, respectively.

The mean clearance of quetiapine in the elderly is approximately 30-50 % lower than that seen in adults aged 18-65 years.

The mean plasma clearance of quetiapine was reduced by approximately 25 % in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1,73m²), but the individual

clearance values are within the range for normal subjects. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5 % excreted in the urine.

Biotransformation

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. Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces. The mean plasma clearance of quetiapine is reduced by approximately 25 % in subjects with hepatic impairment (stable alcoholic cirrhosis). Since quetiapine is extensively metabolised by the liver, higher plasma levels are expected in the hepatically impaired population and dosage adjustment may be needed in these patients.

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.

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 5-50-fold higher than those observed at a dose range of 300-800 mg/day in humans. Based on these *in vitro* results, it is unlikely that co-administration of quetiapine with other medicines will result in clinically significant medicine inhibition of cytochrome P450 mediated metabolism of the other medicine.

Elimination

The elimination half-lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73 % of a radiolabelled drug was excreted in the urine and 21 % in the faeces with less than 5 % of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5 % excreted in the urine.

Special populations

Gender

The pharmacokinetics of quetiapine does 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/1.73 m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment

The mean quetiapine plasma clearance decreases with approximately 25 % in 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).

Paediatric population

Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though Cmax in children was at the higher end of the range observed in adults. The AUC and Cmax for the active metabolite, norquetiapine, were higher, approximately 62 % and 49 % in children (10-12 years), respectively and 28 %and 14 % in adolescents (13-17 years), respectively, compared to adults.

No information is available for **AROQUET XR** in children and adolescents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

AROQUET XR 1**50** *Prolonged-Release tablet core:*

Cellulose

Microcrystalline

Hypromellose

Magnesium stearate

Povidone K30

Sodium chloride

Talc

Film-coating:

Opadry II 85F18422 white consisting of macrogol 3350

Poly Vinyl

Alcohol

Talc

Titanium dioxide

AROQUET XR 50/200/300/400 *Prolonged-release tablet* core:

Hypromellose (K4M)

Hypromellose (100 Premium LV CR)

Sodium chloride

Povidone K30

Isopropyl alcohol

Silicified microcrystalline cellulose

Talc

Magnesium stearate

Film coating:

Opadry II 85F540003 Pink

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

Store at or below 25 °C. Keep the blisters in the outer carton until required for use.

STORE OUT OF REACH OF CHILDREN.

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6.4 Special precautions for storage

This medicine does not contain any special storage conditions.

6.5 Nature and contents of container

AROQUET XR 150 *Prolonged-release tablets* are packed in white opaque PVC/PVdC/Alu blister, Alu-Alu blister with 10, 30, 50, 60 or 100 tablets and white opaque HDPE container with white opaque polypropylene child resistant closure with 60 or 100 tablets.

AROQUET XR 50/200/300/400 *Prolonged-release* tablets are packed in PVC/PVdC/Alu blister pack. Each blister strip contains 10 tablets. Blister strips are packed in an outer cardboard box, containing 10, 30, 50, 60 or 100 tablets per pack.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

Tuscany Office Park, Building 2

6 Coombe Place, Rivonia,

Johannesburg,

South Africa

8. REGISTRATION NUMBER(S)

AROQUET XR 50:48/2.6.5/0011

AROQUET XR 150:52/2.6.5/0998

AROQUET XR 200:48/2.6.5/0012

AROQUET XR 300:48/2.6.5/0013

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AROQUET XR 400:48/2.6.5/0014
9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 6 April 2021
10. DATE OF REVISION OF THE TEXT 6 April 2021