PROFESSIONAL INFORMATION

SCHEDULING STATUS: S5

1. NAME OF THE MEDICINE

NOPTIQUEL™ XR 50 (Prolonged release tablets)

NOPTIQUEL™ XR 150 (Prolonged release tablets)

NOPTIQUEL™ XR 200 (Prolonged release tablets)

NOPTIQUEL™ XR 300 (Prolonged release tablets)

NOPTIQUEL™ XR 400 (Prolonged release tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each NOPTIQUEL XR 50 prolonged release tablet contains quetiapine fumarate, equivalent to 50 mg quetiapine free base.

Each NOPTIQUEL XR 150 prolonged release tablet contains quetiapine fumarate, equivalent to 150 mg quetiapine free base.

Each NOPTIQUEL XR 200 prolonged release tablet contains quetiapine fumarate, equivalent to 200 mg quetiapine free base.

Each NOPTIQUEL XR 300 prolonged release tablet contains quetiapine fumarate, equivalent to 300 mg quetiapine free base.

Each NOPTIQUEL XR 400 prolonged release tablet contains quetiapine fumarate, equivalent to 400 mg quetiapine free base.

NOPTIQUEL XR prolonged release tablets contain sugar (lactose):

Lactose content per tablet:

NOPTIQUEL XR 50:	14,21 mg
NOPTIQUEL XR 150:	42,63 mg
NOPTIQUEL XR 200:	56,84 mg
NOPTIQUEL XR 300:	85,26 mg
NOPTIQUEL XR 400:	113,68 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged release tablet

NOPTIQUEL XR 50 tablets are white to off-white, round biconvex tablets, engraved with “50” on one side and plain on the other side.

NOPTIQUEL XR 150 tablets are white to off-white, oblong biconvex tablets, engraved with “150” on one side and plain on the other side.

NOPTIQUEL XR 200 tablets are white to off-white, oblong biconvex tablets, engraved with “200” on one side and plain on the other side.

NOPTIQUEL XR 300 tablets are white to off-white, oblong biconvex tablets, engraved with “300” on one side and plain on the other side.

NOPTIQUEL XR 400 tablets are white to off-white, oval biconvex tablets, engraved with “400” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NOPTIQUEL XR is indicated for the treatment of:

- Schizophrenia.
- Preventing relapse in stable schizophrenic patients who have been maintained on NOPTIQUEL 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 (mania, 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 NOPTIQUEL XR.

4.2 Posology and method of administration

Posology

Adults

Treatment of schizophrenia:

The initial daily dose 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 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

Treatment of manic episodes associated with bipolar disorder:

The daily dose at 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 to 800 mg per day, depending on the clinical response and tolerability of the patient.

Treatment of depressive episodes associated with bipolar disorder:

NOPTIQUEL XR should be administered once daily in the evening.

NOPTIQUEL XR should be titrated as follows:

50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). NOPTIQUEL XR may be titrated to 400 mg on Day 5 and up to 600 mg by Day 8.

Antidepressant efficacy was demonstrated with quetiapine (as in NOPTIQUEL XR) at 300 mg and 600 mg, however no additional benefit has been reported in the 600 mg group during short-term treatment.

Prevention of recurrence in maintenance treatment of bipolar disorder

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

Patients who have responded to NOPTIQUEL XR for acute treatment of bipolar disorder should continue NOPTIQUEL XR therapy at the same dosing regimen. NOPTIQUEL XR dose may be re-adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 to 800 mg per day.

Treatment of major depressive disorder (MDD):

NOPTIQUEL 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 may be made upwards or downwards within the recommended dose range of 50 to 300 mg, depending upon the clinical response and tolerability of the patient.

For maintenance therapy in MDD the effective dose during initial treatment should be continued. The dose may be adjusted within the recommended dose range, depending upon the clinical response and tolerability of the patient.

Switching from a quetiapine immediate-release tablet:

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

Special populations

Elderly population:

NOPTIQUEL XR should be used with caution in the elderly, especially during the initial dosing period (see section 4.4, “Elderly patients”). The rate of dose-titration of NOPTIQUEL XR may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine may be reduced by 30 to 50 % in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose may be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

In elderly patients with MDD, initial dosing should begin at 50 mg/day on Days 1 to 3; the dose may be increased to 100 mg/day on Day 4 and 150 mg/day on Day 8 and then up to 300 mg/day, depending on clinical response and tolerability.

Paediatric population:

The safety and efficacy of NOPTIQUEL XR has not been evaluated in children and adolescents. NOPTIQUEL XR is therefore not recommended for use in children and adolescents below 18 years of age.

Renal impairment:

Dose adjustment is not necessary in patients with renal impairment.

Hepatic impairment:

Quetiapine is extensively metabolised by the liver. Therefore, NOPTIQUEL 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 with 50 mg/day. The dose may be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

Method of administration

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

4.3 Contraindications

- Known hypersensitivity to quetiapine fumarate, or to any component of NOPTIQUEL XR (see section 6.1).
- Elderly patients with dementia, exhibiting behavioural disturbances.
- Co-administration with 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

Elderly patients with dementia

NOPTIQUEL XR is not approved for the treatment of elderly patients with dementia, exhibiting behavioural disturbances (see section 4.3). Elderly patients with dementia-related psychosis are at an increased risk of death, compared to placebo.

Before prescribing, medical practitioners are advised to carefully assess the risks and benefits of the use of atypical antipsychotics in elderly patients with dementia, considering risk predictions for stroke in the individual patients (e.g. hypertension, diabetes, current smoking, atrial fibrillation and age > 80 years).

Dysphagia

Dysphagia and aspiration (see section 4.8) have been reported with quetiapine and it should therefore be used with caution in patients at risk of 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.

Metabolic risk and endocrine effects

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see “Hyperglycaemia and diabetes mellitus”) and lipids, patients' metabolic parameters should be assessed at the time of treatment initiation and changes in these

parameters should be regularly controlled during treatment. Worsening in these parameters should be managed as clinically appropriate.

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 NOPTIQUEL XR (see section 4.8).

Patients with an established diagnosis of diabetes mellitus who are started on NOPTIQUEL XR 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 started on NOPTIQUEL XR should be monitored regularly for worsening of glucose control or for emerging symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with NOPTIQUEL XR should undergo fasting blood glucose testing.

In some cases, hyperglycaemia may be resolved when NOPTIQUEL XR is discontinued; however, some patients require continuation of antidiabetic treatment despite discontinuation of NOPTIQUEL XR.

Weight gain

Weight gain frequently occurs, particularly during early treatment. Weight should be monitored and managed as clinically appropriate and in accordance with antipsychotic guidelines (see section 4.8).

Lipids

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol may occur with NOPTIQUEL XR (see section 4.8). Lipid changes should be managed as clinically appropriate.

Pancreatitis

Pancreatitis has been reported, mainly in patients with increased triglycerides, gallstones and with alcohol consumption.

Thyroid hormone levels

NOPTIQUEL XR treatment is 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 is maximal within the first 2 to 4 weeks of quetiapine (as in NOPTIQUEL XR) treatment, with no further reduction during long-term treatment.

There is no evidence of clinically significant changes in thyroid stimulating hormone (TSH) concentration over time. In nearly all cases, cessation of NOPTIQUEL XR treatment is associated with a reversal of the effects on total and free T_4, irrespective of the duration of treatment.

Smaller decreases in total T_3 and reverse T_3 occur only at higher doses. Levels of thyroxine binding globulin (TBG) are unchanged and in general, reciprocal increases in TSH are not observed, with any indication that NOPTIQUEL XR causes clinically relevant hypothyroidism.

Neutropenia and agranulocytosis

Severe neutropenia (neutrophil count < 0,5 X 10^9/L) has been reported in quetiapine (as in NOPTIQUEL XR). Most cases of severe neutropenia have occurred within a couple of months of starting therapy. 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. NOPTIQUEL XR 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 therapy with NOPTIQUEL XR. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

QT prolongation

QT prolongation has been reported (see sections 4.8 and 4.9).

Caution should be exercised in patients with cardiovascular disease or family history of QT prolongation.

Caution should also be exercised if NOPTIQUEL XR is prescribed either with medicines known to increase QT interval, or with concomitant antipsychotics, 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).

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 NOPTIQUEL XR should be reassessed in patients with suspected cardiomyopathy or myocarditis.

Somnolence

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

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 and dizziness

NOPTIQUEL XR may induce 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 NOPTIQUEL XR.

NOPTIQUEL XR 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.

Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicines (such as NOPTIQUEL XR). Since patients treated with these medicines often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with NOPTIQUEL XR and preventive measures should be undertaken.

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. Improvement may not occur during the first few weeks or more of treatment, patients should therefore be closely monitored until such improvement occurs. The risk of suicide may increase in the initial stages of recovery.

Medical practitioners should also consider the potential risk of suicide-related events after abrupt cessation of NOPTIQUEL XR treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which NOPTIQUEL 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 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 be monitored closely for the emergence of worsening of depression, suicidal thoughts or behaviour, or any unusual changes in mood or behaviour.

Neuroleptic malignant syndrome (NMS)

NMS has been associated with antipsychotic treatment, including NOPTIQUEL XR treatment (see section 4.8). Clinical manifestations include altered mental status, hyperthermia, muscular rigidity, autonomic instability and increased creatine phosphokinase. In such an event, NOPTIQUEL XR should be discontinued and appropriate medical treatment given.

Tardive dyskinesia / extrapyramidal symptoms (TD/EPS)

Tardive dyskinesia is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medicines including NOPTIQUEL XR. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of NOPTIQUEL XR should be considered. The symptoms of tardive dyskinesia may worsen or even arise after discontinuation of treatment (see section 4.8).

In schizophrenia and bipolar mania, the incidence of extrapyramidal symptoms is not different from placebo. In bipolar depression and major depressive disorder NOPTIQUEL XR may cause an increased incidence of extrapyramidal side effects (see section 4.8).

The use of quetiapine (as in NOPTIQUEL XR) 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.

Seizures

No data is available about the incidence of seizures in patients with a history of seizure disorder. NOPTIQUEL XR should however be used with caution in patients with a history of seizures, or a decreased seizure threshold.

Sleep apnoea syndrome

Sleep apnoea syndrome has been reported in patients taking NOPTIQUEL XR (see section 4.8). 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, NOPTIQUEL XR should be used with caution.

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, vomiting, headache, dizziness and irritability have been described after abrupt cessation of antipsychotic medicines, including NOPTIQUEL XR. Gradual withdrawal of NOPTIQUEL XR, over a period of at least 1 to 2 weeks is recommended (see section 4.8).

Misuse and abuse

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

Anticholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to side effects reflecting anticholinergic effects when NOPTIQUEL XR is used at recommended doses, when used concomitantly with other medicines having anticholinergic effects, and in the setting of overdose. NOPTIQUEL XR should be used with caution in patients receiving medicines having anticholinergic (muscarinic) effects (see section 4.5).

NOPTIQUEL XR should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see section 4.8).

Interactions

See also section 4.5.

Concomitant use of quetiapine (as in NOPTIQUEL XR) with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate). Higher doses of NOPTIQUEL XR may need to be considered if used concomitantly with these medicines. See section 4.8.

Concomitant use of NOPTIQUEL XR and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and HIV-protease inhibitors) may significantly increase plasma concentrations of quetiapine and is contraindicated (see section 4.3 and 4.5). Lower doses of NOPTIQUEL XR should therefore be used. 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.

Special populations

Paediatric population

NOPTIQUEL XR 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.

Elderly patients (65 years and older)

Where the use of antipsychotics in the elderly is considered essential, the lowest effective dose should be used. These patients should be carefully monitored to avoid or reduce hypotension, gait disturbances, over sedation and complications associated with hyperglycaemia (see “Hyperglycaemia and diabetes mellitus”).

Hepatic function impairment

NOPTIQUEL XR should be used with caution in patients with hepatic impairment.

Since quetiapine is extensively metabolised by the liver, higher blood concentrations of quetiapine may occur, dosage adjustment may be necessary, especially in the initial dosing period. (See section 4.2).

Lactose

NOPTIQUEL XR tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take NOPTIQUEL XR.

4.5 Interactions with other medicines and other forms of interaction

Cytochrome CYP3A4 inhibitors

CYP3A4 is the main enzyme responsible for cytochrome P450-mediated metabolism of quetiapine, as in NOPTIQUEL XR.

Concomitant use of NOPTIQUEL XR and potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics such as erythromycin, clarithromycin and nefazodone, and

HIV-protease inhibitors) may significantly increase plasma concentrations of quetiapine and is contraindicated (see section 4.3).

The consumption of grapefruit juice while taking NOPTIQUEL XR is contraindicated (see section 4.3).

The pharmacokinetics of NOPTIQUEL XR are not altered following co-administration with cimetidine (a known P450 enzyme inhibitor).

Cytochrome CYP3A4 inducers

Quetiapine does not induce the hepatic enzyme systems involved in the metabolism of antipyrine.

Co-administration of carbamazepine significantly increases the clearance of quetiapine and reduces systemic quetiapine exposure (as measured by AUC) to an average of 13 % of the exposure during administration of quetiapine alone; although a greater effect can be seen in some patients. This could affect the efficacy of NOPTIQUEL XR therapy.

Co-administration with phenytoin (another microsomal enzyme inducer) causes a greatly increased clearance of quetiapine by approximately 450 %. In patients receiving a hepatic enzyme inducer, initiation of NOPTIQUEL XR treatment should only occur if the medical practitioner 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 and “Anticonvulsants” below).

Medicines that prolong the QT interval

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

Anticholinergics

NOPTIQUEL XR should be used with caution in patients receiving medicines having anticholinergic (muscarinic) effects (see section 4.4).

Centrally acting medicines and alcohol

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

Anticonvulsants

The pharmacokinetics of sodium valproate and NOPTIQUEL XR are not altered to a clinically relevant extent when co-administered.

Antidepressants

The pharmacokinetics of NOPTIQUEL XR are not significantly altered following co-administration with imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

Lithium

The pharmacokinetics of lithium are not altered when co-administered with NOPTIQUEL XR; however, the incidence of extrapyramidal effects (particularly tremor), somnolence and weight gain is higher when NOPTIQUEL XR is taken with lithium, than when used alone.

Antipsychotics

The pharmacokinetics of NOPTIQUEL XR are not significantly altered following co-administration with risperidone and haloperidol. However, concomitant administration of thioridazine increases clearance of quetiapine with approximately 70 %.

Laboratory results

False positive results in enzyme immunoassays for methadone and tricyclic antidepressants have been reported in patients who have taken quetiapine (as in NOPTIQUEL XR).

Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

Special populations

A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

No interaction studies have been performed in special groups.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breastfeeding

NOPTIQUEL XR is distributed into breast milk; the degree to which it is distributed is unknown. Women should be advised to avoid breastfeeding their babies while taking NOPTIQUEL XR.

Fertility

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

4.7 Effects on ability to drive and use machines

NOPTIQUEL XR may cause somnolence and dizziness. Patients should be cautioned not to drive, operate hazardous machinery or perform hazardous tasks, while taking NOPTIQUEL XR.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse events with quetiapine 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.

Tabulated list of adverse reactions

Infections and infestations

Frequent: Urinary tract infection[18]

Immune system disorders

Less frequent: Hypersensitivity[7], anaphylactic reaction[19], angioedema

Blood and lymphatic system disorders

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

Less frequent: Neutropenia, thrombocytopenia, anaemia, decreased platelet count[14], agranulocytosis

Endocrine disorders

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

Less frequent: Decreases in free T_3, hypothyroidism, inappropriate antidiuretic hormone (ADH) secretion

Metabolism and nutritional disorders

Frequent: Increased serum triglyceride levels[11], elevations in total cholesterol (predominantly LDL cholesterol)[12], decreases in HDL cholesterol[17],

	weight gain, increased appetite, blood glucose increased to hyperglycaemic levels [8]
Less frequent:	Hyponatraemia, diabetes mellitus, exacerbation of pre-existing diabetes, metabolic syndrome

Psychiatric disorders

Frequent:	Abnormal dreams, nightmares, suicidal ideation and suicidal behaviour (see section 4.4), somnolence[16]
Less frequent:	Somnambulism and related reactions such as sleep talking and sleep related eating disorder

Nervous system disorders

Frequent:	Dizziness[6, 16], headache[16], extrapyramidal symptoms[1, 16], dysarthria
Less frequent:	Seizure[1], restless legs syndrome; tardive dyskinesia, syncope [6, 16], parkinsonian symptoms, neuroleptic malignant syndrome [1] (see section 4.4)

Eye disorders

Less frequent:	Blurred/abnormal vision

Vascular disorders

Frequent:	Orthostatic hypotension[1, 6, 16]
Less frequent:	Venous thromboembolism (see section 4.4)
Frequency unknown:	Stroke

Cardiac disorders

Frequent:	Tachycardia[6], palpitations
Less frequent:	Prolongation of the QTc interval (see section 4.4), bradycardia

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea

Less frequent: Rhinitis

Gastro-intestinal disorders

Frequent: Dry mouth, constipation, dyspepsia, vomiting

Less frequent: Dysphagia[9], pancreatitis, intestinal obstruction/ileus

Hepato-biliary disorders

Frequent: Elevations in serum alanine amino-transferase (AST), elevations in gamma-GT levels[5]

Less frequent: Elevations in serum aspartate amino-transferase (AST), jaundice, hepatitis

Skin and subcutaneous tissue disorders

Less frequent: Stevens Johnson syndrome

Frequency unknown: Erythema multiforme, toxic epidermal necrolysis, Drug Reaction 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: Neonatal medicine withdrawal syndrome

Reproductive system and breast disorders

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

General disorders and administration site disorders

Frequent: Withdrawal (discontinuation) symptoms[1, 10], asthenia, peripheral oedema, irritability, pyrexia

Less frequent: Hypothermia

Investigations

Frequent: Increase in serum prolactin[15]

Less frequent: Elevations in blood creatine phosphokinase[13]

NOTES:

1) See section 4.4.
2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of NOPTIQUEL XR.
3) Shift in neutrophils from ≥ 1,5 x 10^9/L at baseline to < 0,5 x 10^9/L at any time during treatment.
4) Based on ≥ 7 % increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
5) Elevations 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.
6) NOPTIQUEL XR may induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (See section 4.4).
7) Manifestations of hypersensitivity may include angioedema and urticaria/rash.
8) Fasting blood glucose ≥ 7,0 mmol/L or a non-fasting blood glucose ≥ 11,1 mmol/L on at least one occasion.
9) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in bipolar depression.
10) The following withdrawal symptoms have been observed most frequently: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

11) Triglycerides ≥ 200 mg/dl on at least one occasion (patients ≥ 18 years of age).
12) Cholesterol ≥ 240 mg/dl on at least one occasion (patients ≥ 18 years of age).
13) Adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
14) Platelets ≤ 100 x 10^9/L on at least one occasion.
15) Prolactin levels (patients > 18 years of age): > 20 µg/L for males; > 30 µg/L for females at any time.
16) May lead to falls.
17) HDL cholesterol: < 40 mg/dl for males; < 50 mg/dl for females at any time.
18) Causality with NOPTIQUEL XR has not been established.
19) Based on post-marketing published reports.

Description of selected adverse reactions

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 (contained in NOPTIQUEL XR) treatment.

Paediatric population

The safety and efficacy of NOPTIQUEL XR has not been evaluated in children and adolescents. See sections 4.1 and 4.4.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP

(Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

4.9 Overdose

Symptoms

Overdose of quetiapine alone (as in NOPTIQUEL XR), that resulted in death or coma has been reported.

Death has been reported following an acute overdose of 13,6 g quetiapine alone. However, survival has also been reported following acute overdoses of up to 30 g.

Cases of QT prolongation with overdose have been reported (see section 4.4 and 4.8). Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effect of overdose (see section 4.4, “Concomitant illness”).

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 and hypotension (see section 4.8).

Management

There is no specific antidote to quetiapine. In cases of severe intoxication, the possibility of multiple medicines involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

2.6.5 Central nervous system depressants: Miscellaneous structures.

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines

ATC code: N05A H04

Quetiapine is an atypical antipsychotic medicine. Quetiapine and the active metabolite norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for serotonin 5-HT_2 and dopamine D_1- and D_2-receptors in the brain. The combination of quetiapine's higher selectivity for serotonin (5-HT_2) receptors than for dopamine D_2-receptors, and its antagonistic action at these receptors reportedly contributes to the clinical antipsychotic properties of quetiapine.

Norquetiapine also has high affinity for the noradrenaline transporter (NET).

Both quetiapine and norquetiapine have a high affinity for histamine H_1 and adrenergic $alpha_1$ receptors, with a lower affinity at adrenergic $alpha_2$ and serotonin 5-HT_1A- receptors.

Quetiapine has no appreciable affinity for cholinergic muscarinic or benzodiazepine receptors.

5.2 Pharmacokinetic properties

Absorption and distribution

Quetiapine is absorbed and extensively metabolised after oral doses.

The bioavailability of quetiapine is not significantly affected by a light meal, however, C_{max} and AUC are statistically significantly increased by a high fat meal. This increase in exposure is not clinically significant and therefore NOPTIQUEL XR may be taken with or without food.

Quetiapine is about 83 % bound to plasma proteins.

Steady-state peak molar concentrations of the active metabolite norquetiapine are about 35 % of that of quetiapine.

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

Biotransformation

Quetiapine is extensively metabolised by the liver through multiple pathways; the parent compound accounts for less than 5 % of unchanged medicine-related material in the urine or faeces, as determined by radiolabelled quetiapine. Norquetiapine is the active metabolite.

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) are weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities *in vitro*, but only at concentrations approximately 5 to 50-fold higher than those observed in the usual effective dose range of 300 to 800 mg/day in humans. Based on these results, it is unlikely that co-administration of quetiapine and 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.

Linearity/non-linearity

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dose range. NOPTIQUEL XR displays dose-proportional pharmacokinetics for doses of up to 800 mg taken once daily.

Pharmacokinetics in special patient groups

Elderly patients

The mean clearance of quetiapine in the elderly, 65 years of age and over, is about 30 - 50 % less than in healthy adults aged 18 to 65 years.

Paediatric patients

The safety and efficacy of NOPTIQUEL XR have not been evaluated in children.

Gender

There appears to be no difference between men and women in the kinetics of quetiapine.

Renal impairment

The mean plasma clearance of quetiapine is reduced by about 25 % in patients with severe renal impairment (creatinine clearance less than 30 ml/min per 1,73 m^2), but the individual clearance values are within the range for normal patients. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5 % excreted in the urine.

Hepatic impairment

Since quetiapine is extensively metabolised by the liver higher plasma levels are expected in the hepatically impaired population.

The mean plasma clearance of quetiapine is reduced by approximately 25 % in patients with hepatic impairment (stable alcoholic cirrhosis).

Dosage adjustment may be required for these patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Crystalline maltose, lactose, magnesium stearate, methacrylic acid-ethyl acrylate copolymer, talc, triethyl citrate.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Prolonged release tablets: 36 months

Bottles: Use within 60 days of opening.

6.4 Special precautions for storage

Store in the original packaging, at or below 30 °C. Keep the blisters in the carton until required for use. Keep bottles tightly closed.

6.5 Nature and contents of container

NOPTIQUEL XR tablet range is packed in:

A cardboard box containing 10, 30, 60 or 100 tablets, packed in white opaque PVC/PCTFE-aluminium foil blister strips.

White opaque HDPE bottles, with child resistant polypropylene (PP) screw caps and induction seal liners containing 10, 30, 60 or 100 tablets.

Not all pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATES OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd

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617 Rubenstein Drive

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8. REGISTRATION NUMBERS

NOPTIQUEL XR 50: 53/2.6.5/0318.313

NOPTIQUEL XR 150: 53/2.6.5/0319.314

NOPTIQUEL XR 200: 53/2.6.5/0320.315

NOPTIQUEL XR 300: 53/2.6.5/0321.316

NOPTIQUEL XR 400: 53/2.6.5/0322.317

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Registration date: 05 November 2024

10. DATE OF REVISION OF THIS TEXT

Not applicable