

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1 NAME OF THE MEDICINE

DOPAQUEL 25 (film-coated tablet)

DOPAQUEL 100 (film-coated tablet)

DOPAQUEL 200 (film-coated tablet)

DOPAQUEL 300 (film-coated tablet)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

DOPAQUEL 25: Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 25 mg.

DOPAQUEL 100: Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 100 mg.

DOPAQUEL 200: Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 200 mg.

DOPAQUEL 300: Each film-coated tablet contains quetiapine fumarate equivalent to quetiapine 300 mg.

Excipients with known effects:

Contains sugar: Lactose monohydrate

DOPAQUEL 25 contains sugar (19,821 mg lactose monohydrate per tablet).

DOPAQUEL 100 contains sugar (79,285 mg lactose monohydrate per tablet).

DOPAQUEL 200 contains sugar (158,569 mg lactose monohydrate per tablet).

DOPAQUEL 300 contains sugar (237,854 mg lactose monohydrate per tablet).

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

DOPAQUEL 25: White, round, biconvex, film-coated tablets debossed with 'R' on one side

and '1' on the other side.

DOPAQUEL 100: Yellow, round, biconvex, film-coated tablets debossed with 'R' on one side and '3' on the other side.

DOPAQUEL 200: White, round, biconvex, film-coated tablets debossed with 'R' on one side and '5' on the other side.

DOPAQUEL 300: White, modified capsule shaped, biconvex, film-coated tablets debossed with 'R' on one side and '6' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

DOPAQUEL is indicated for the treatment of schizophrenia.

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

Safety and efficacy beyond 12 weeks has not been demonstrated.

4.2 Posology and method of administration

Posology

DOPAQUEL should be administered twice daily, with or without food.

Adults:

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

From Day 4 onwards, the dose should be titrated to the effective dose range of 300 - 450 mg/day.

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

For the treatment of manic episodes associated with bipolar disorder, the total daily dose for the first 4 days of therapy is 100 mg (Day 1), 200 mg (Day 2), 300 mg (Day 3) and 400 mg (Day 4). Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day.

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

Special Populations

Elderly:

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

Renal and hepatic impairment:

The oral clearance of DOPAQUEL is reduced by approximately 25 % in patients with renal or hepatic impairment. Quetiapine is extensively metabolised by the liver, and therefore should be used with caution in patients with known hepatic impairment.

Patients with renal or hepatic impairment should be started on DOPAQUEL 25 mg/day. The dose should be increased daily in increments of 25 - 50 mg, to an effective dose.

Method of administration

Oral administration.

4.3 Contraindications

DOPAQUEL is contraindicated in:

Patients who are hypersensitive to quetiapine or to any of the excipients listed in section 6.1.

Pregnancy and lactation, as safety has not been demonstrated.

Advanced liver and renal function impairment, as safety has not been demonstrated.

Children and adolescents below the age of 18 years as safety and efficacy have not been demonstrated.

Co-administration with cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents, erythromycin and clarithromycin and nefazodone, is contraindicated (see section 4.5).

DOPAQUEL is not indicated for use in elderly patients with dementia-related psychosis.

4.4 Special warnings and precautions for use

Paediatric population:

DOPAQUEL 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. In addition to the known safety profile identified in adults, certain adverse events occurred at a higher frequency in children and adolescents compared

to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents. Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

DOPAQUEL is associated with an increased incidence of extrapyramidal symptoms (EPS) in children and adolescents.

Suicide/suicidal thoughts or clinical worsening:

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

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

Other psychiatric conditions for which DOPAQUEL is prescribed can also be associated with an increased risk of suicide-related events. In addition, these conditions may be co-morbid with major depression 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 suicidal attempts, and should receive careful monitoring during treatment.

Close supervision of patients and in particular those at high risk should accompany medicine therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or ideation and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

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 DOPAQUEL.

Patients with an established diagnosis of diabetes mellitus who are started on DOPAQUEL, 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 DOPAQUEL should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness.

Patients who develop symptoms of hyperglycaemia during treatment with DOPAQUEL should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when DOPAQUEL was discontinued, however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect medicine.

Metabolic risk:

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 for during the course of treatment.

Worsening in these parameters should be managed as clinically appropriate.

Pancreatitis:

Pancreatitis has been reported in clinical trials and during the post marketing experience. Among the 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 Lipids), gallstones and alcohol consumption.

Extrapyramidal symptoms:

DOPAQUEL has been associated with an increased incidence of extrapyramidal symptoms (EPS) in patients treated for major depressive episodes in bipolar disorder (see section 4.8).

The use of DOPAQUEL 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.

Tardive dyskinesia:

There is a potential for DOPAQUEL to cause tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, discontinuation of DOPAQUEL should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8).

Somnolence:

DOPAQUEL treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of DOPAQUEL.

Orthostatic hypotension:

DOPAQUEL may induce orthostatic hypotension and related dizziness (see section 4.8), especially during the initial dose-titration period; this is more common in elderly patients than in younger patients.

This could increase the occurrence of accidental injury (fall), especially in the elderly.

DOPAQUEL 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, DOPAQUEL should be used with caution.

Seizures:

Caution is recommended when treating patients with a history of seizures (see section 4.8).

Neuroleptic malignant syndrome:

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

Serotonin syndrome:

Concomitant administration of DOPAQUEL and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptakeinhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors

(SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Severe neutropenia and agranulocytosis:

Severe cases of neutropenia (neutrophil count $< 0,5 \times 10^9/\text{litre}$) have been reported with DOPAQUEL. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with DOPAQUEL. There is no apparent dose relationship. Resolution of leucopenia and/or neutropenia may follow cessation of therapy with DOPAQUEL. Some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count and history of medicine induced neutropenia. However, some cases have occurred in patients without pre-existing risk factors. DOPAQUEL should be discontinued in patients with a neutrophil count $< 1,0 \times 10^9/\text{litre}$. These patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed $1,5 \times 10^9/\text{litre}$).

Neutropenia should be considered in patients presenting with fever or infection, 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 DOPAQUEL therapy. Such patients should have a white blood cell count and an absolute neutrophil count performed promptly, especially in the absence of predisposing factors.

Weight:

Weight gain has been reported in patients who have been treated with DOPAQUEL, and should be monitored and managed as clinically appropriate.

Weight gain occurs predominantly during the early weeks of treatment.

Lipids:

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

QT prolongation:

QT prolongation has been reported with quetiapine, as in DOPAQUEL at the therapeutic doses (see section 4.8) and in overdose (see section 4.9). Caution should be exercised when DOPAQUEL is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when DOPAQUEL 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).

Cardiomyopathy and myocarditis:

Cardiomyopathy and myocarditis have been reported.

In patients with suspected cardiomyopathy or myocarditis discontinuation of DOPAQUEL should be considered.

Elderly patients with dementia-related psychosis:

DOPAQUEL is not approved for the treatment of patients with dementia-related psychosis. With some atypical antipsychotics, an approximately 3-fold increased risk of cerebrovascular adverse events has been seen in the dementia population. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. DOPAQUEL should be used with caution in patients with risk factors for stroke.

Elderly patients with Parkinson's disease (PD)/parkinsonism:

Caution should be exercised if DOPAQUEL is prescribed to elderly patients with PD.

Elderly patients:

Where the use of DOPAQUEL 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.

Dysphagia:

Dysphagia (see section 4.8) and aspiration have been reported with quetiapine, as in DOPAQUEL. DOPAQUEL should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction:

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine, as in DOPAQUEL (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 DOPAQUEL and preventive measures undertaken.

Severe Cutaneous Adverse Reactions:

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalised Exanthematous Pustulosis (AGEP), Erythema multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) are potentially life-threatening adverse drug reactions that have been reported during quetiapine exposure.

SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Discontinue DOPAQUEL if severe cutaneous adverse reactions occur.

Withdrawal:

Acute withdrawal symptoms including nausea, vomiting, headache, diarrhoea, dizziness, irritability and insomnia have been described after abrupt cessation of DOPAQUEL. Recurrence of psychotic symptoms may also occur and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesias) have been reported. Gradual withdrawal over a period of at least one to two weeks is advisable.

Misuse and abuse:

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

Anticholinergic (muscarinic) effects:

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to adverse drug reactions (ADRs) reflecting anticholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anticholinergic effects, and in the setting of overdose. DOPAQUEL should be used with caution in patients receiving medications having anticholinergic (muscarinic) effects. DOPAQUEL should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see section 4.5, 4.8 and 4.9).

Interactions:

See section 4.5.

Concomitant use of DOPAQUEL with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine, as in DOPAQUEL, therapy. In patients receiving a hepatic enzyme inducer, initiation of DOPAQUEL 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).

Additional information:

Data of quetiapine, as in DOPAQUEL, in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3.

Lactose:

DOPAQUEL film-coated tablets contain lactose. Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicines and other forms of interaction

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

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

DOPAQUEL may antagonise the actions of dopaminergics, such as levodopa.

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

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

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

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. However, co-administration of quetiapine and thioridazine caused increases in clearance of quetiapine as in DOPAQUEL.

DOPAQUEL should be used with caution in combination with serotonergic medicines, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Quetiapine as in DOPAQUEL did not induce the hepatic enzyme systems involved in the metabolism of antipyrine. In a multiple dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13 % of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, and hence in each patient, consideration for a higher dose of DOPAQUEL, depending on clinical response, should be considered. It should be noted that the recommended maximum daily

dose of DOPAQUEL is 750 mg/day, for the treatment of schizophrenia, and 800 mg/day for the treatment of manic episodes associated with bipolar disorder. Continued treatment at higher doses should only be considered as a result of careful consideration of the benefit-risk assessment for an individual patient.

Co-administration of quetiapine with another microsomal enzyme inducer, phenytoin, also caused increases in clearance of quetiapine.

Increased doses of DOPAQUEL may be required to maintain control of psychotic symptoms in patients co-administered DOPAQUEL and phenytoin and other hepatic enzyme inducers (e.g. barbiturates, rifampicin etc.). The dose of DOPAQUEL may need to be reduced if phenytoin, carbamazepine or other hepatic enzyme inducers are withdrawn and replaced with a non-inducer (e.g. sodium valproate).

CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. The pharmacokinetics of quetiapine was not altered following co-administration with cimetidine, a known P450 enzyme inhibitor. The pharmacokinetics of quetiapine as in DOPAQUEL were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

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 as in DOPAQUEL. On the basis of this, concomitant use of DOPAQUEL with CYP3A4 inhibitors (such as HIV protease inhibitors,azole antifungals and macrolide antibiotics) is contraindicated (see section 4.3). It is also not recommended to consume grapefruit juice while on DOPAQUEL therapy as serum concentration may be increased.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

DOPAQUEL is contra-indicated during pregnancy and lactation, as safety has not been demonstrated (see section 4.3).

Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported.

Breastfeeding

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent.

4.7 Effects on ability to drive and use machines

DOPAQUEL may cause somnolence which may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility is known.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) with DOPAQUEL 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.

Adverse reactions arranged by system organ class are as follows:

Blood and the lymphatic system disorders

Frequent: Leucopenia (see section 4.4), decreased haemoglobin, decreased neutrophil count, increased eosinophils.

Less frequent: neutropenia (see section 4.4), thrombocytopenia, anaemia, decreased platelet count, agranulocytosis

Immune system disorders

Less frequent: Hypersensitivity (angioedema, anaphylaxis, urticaria / rash), anaphylactic reaction

Endocrine disorders

Frequent: Hyperprolactinaemia, decreases in total T₄, decreases in free T₄, decreases in total T₃, increases in TSH.

Less frequent: Inappropriate antidiuretic hormone secretion, hypothyroidism, decreases in free T₃.

Metabolism and nutrition disorders

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

Less frequent: Diabetes mellitus (or exacerbation of pre-existing diabetes), hyponatraemia, metabolic syndrome.

Psychiatric disorders

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

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

Nervous system disorders

Frequent: Headache, somnolence (see section 4.4), dizziness (see section 4.4), anxiety, extrapyramidal symptoms (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity and tremor), dysarthria

Less frequent: Seizures (see section 4.4), tardive dyskinesia, restless legs syndrome, syncope (see section 4.4), confusional state

Eye disorders

Frequent: Blurred vision

Frequency not known: Dry eyes, asymptomatic changes in lenses of the eyes with long term use

Ear and labyrinth disorders

Less frequent: Ear pain

Cardiac disorders

Frequent: Tachycardia, palpitations

Less frequent: QTc prolongation (see section 4.4), chest pain, bradycardia

Frequency unknown: Cardiomyopathy and myocarditis

Vascular disorders

Frequent: Orthostatic hypotension (associated with dizziness, tachycardia and syncope in some patients). See section 4.4.

Less frequent: Venous thromboembolism

Frequency unknown: Stroke

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea

Less frequent: Rhinitis

Gastrointestinal disorders

Frequent: Dry mouth, constipation, dyspepsia, vomiting

Less frequent: Diarrhoea, abdominal pain, dysphagia, pancreatitis, intestinal obstruction/ileus

Hepato-biliary disorders

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

Less frequent: Jaundice, hepatitis, elevations in serum aspartate aminotransferase (AST).

Skin and subcutaneous tissue disorders

Less frequent: Angioedema, Stevens-Johnson syndrome

Frequency not known: Toxic epidermal necrolysis, erythema multiforme, acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), cutaneous vasculitis.

Musculoskeletal, connective tissue and bone disorders

Less frequent: Myalgia, rhabdomyolysis, back pain

Renal and urinary disorders

Less frequent: Urinary tract infection, urinary retention

Pregnancy, puerperium and perinatal conditions

Frequency not known: Drug withdrawal syndrome neonatal

Reproductive system and breast disorders

Less frequent: Priapism, galactorrhoea, sexual dysfunction, breast swelling, menstrual disorder

General disorders and administration site conditions

Frequent: Asthenia, peripheral oedema, pyrexia, irritability, withdrawal (discontinuation) symptoms (see section 4.4)

Less frequent: Neuroleptic malignant syndrome (see section 4.4), hypothermia

Investigations

Less frequent: Elevations in blood creatinine phosphokinase.

DOPAQUEL was associated with dose-related decreases in thyroid hormone levels, particularly total T₄ and free T₄. The reduction in total T₄ and free T₄ was maximal within the first 6 weeks of

DOPAQUEL treatment, with no further reduction during long-term treatment. There was no evidence of clinically significant changes in TSH concentration over time. In nearly all cases, cessation of DOPAQUEL treatment has been associated with a reversal of the effects on total and free T₄, irrespective of the duration of treatment. Smaller decreases in total T₃ and reverse T₃ 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 DOPAQUEL causes clinically relevant hypothyroidism.

Elevations in serum transaminase (ALT, AST) or gamma-GT-levels observed in patients administered DOPAQUEL, were usually reversible on continued DOPAQUEL 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

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the pharmacological effects i.e. drowsiness, sedation, tachycardia, hypotension and anticholinergic effects.

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see section 4.4, Orthostatic hypotension).

Management of overdose

There is no specific antidote to DOPAQUEL. Treatment is symptomatic and supportive. 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.

Based on public literature, patients with delirium and agitation and a clear anti-cholinergic syndrome may be treated with physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

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

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

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification:

A. 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 agent which interacts with a broad range of neurotransmitter receptors. Quetiapine exhibits a higher affinity for serotonin (5HT₂) receptors in the brain than it does for dopamine D₁ and D₂ 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.

Quetiapine does not produce sustained elevations in prolactin in man.

Quetiapine, when given twice a day, maintains 5HT₂ and D₂ receptor occupancy for up to 12 hours after dosing.

5.2 Pharmacokinetic properties

After oral administration quetiapine is absorbed and extensively metabolised. The principal human plasma metabolites do not have significant pharmacological activity. The bioavailability of quetiapine is not significantly affected by administration with food. The elimination half-life of quetiapine is approximately 7 hours. Quetiapine is approximately 65 % - 83 % bound to plasma proteins.

The pharmacokinetics of quetiapine are variable but do not differ significantly between men and women.

The mean clearance of quetiapine in the elderly is approximately 30 % to 50 % lower than that seen in adults aged 18 to 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/1,73 m²) and in subjects with hepatic impairment (stable alcoholic cirrhosis), but the individual clearance values are within the range for normal subjects.

Quetiapine is extensively metabolised with parent compound accounting for less than 5 % of unchanged medicine related material in the urine or faeces, following the administration of radio-labelled quetiapine. Approximately 73 % of the radioactivity is excreted in the urine and 21 % in the faeces.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Colloidal silicon dioxide

Dibasic calcium phosphate dihydrate

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Povidone

Sodium starch glycolate.

Coating:

Opadry® white: hypromellose, macrogol and titanium dioxide (25, 200, 300 mg film-coated tablets)

Opadry® yellow: hypromellose, iron oxide yellow, macrogol and titanium dioxide (100 mg film-coated tablets).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep the blisters in the carton until required for use.

Keep the HDPE containers tightly closed.

Keep tablets in the original container.

KEEP OUT OF THE REACH OF CHILDREN

6.5 Nature and contents of container

- DOPAQUEL 25:** 30, 60, 100 or 500 film-coated tablets in white HDPE containers.
Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.
- DOPAQUEL 100:** 30, 60, 90, 100 or 500 film-coated tablets in white HDPE containers.
Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.
- DOPAQUEL 200:** 30, 60, 100 or 500 film-coated tablets in white HDPE containers.
Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.
- DOPAQUEL 300:** 30, 60, 100 or 500 film-coated tablets in white HDPE containers.
Transparent PVC/PVdC/paper backed Alu blister strips containing 7, 10, 14, 28 or 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8 REGISTRATION NUMBERS

DOPAQUEL 25: 43/2.6.5/0429

DOPAQUEL 100: 43/2.6.5/0430

DOPAQUEL 200: 43/2.6.5/0431

DOPAQUEL 300: 43/2.6.5/0432

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02 June 2017

10 DATE OF REVISION OF TEXT

13 January 2025