

SUMMONARY OF PRODUCT CHARACTERISTIC

1. NAME OF THE MEDICINAL PRODUCT

GYREX® 400 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug Substance:

460.52 quetiapine fumarate, equivalent to 400 mg quetiapine

Excipient(s):

Lactose monohydrate (bovine origin) 82.8 mg

See 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film coated tablet.

Yellow, round, curved, film-coated tablets with the “Q400” logo on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

GYREX® is indicated for the treatment of schizophrenia.

GYREX® is indicated for the treatment of bipolar disorder:

- Treatment of moderate to severe episodes of mania in bipolar disorder
- Treatment of major depressive episodes accompanying bipolar disorder
- Prevention of recurrence of manic or depressive episodes in patients with bipolar disorder who have previously responded to quetiapine treatment.

4.2. Posology and method of administration

Posology/frequency and duration of administration:

Different dosing schemes are available for each indication. Clear information should therefore be provided to ensure that patients receive the dose appropriate to their circumstances.

GYREX® can be taken with or without food.

Adults

Treatment of schizophrenia

In the treatment of schizophrenia, GYREX® should be taken 2 times a day. The total daily doses to be taken in the first 4 days of treatment are 50 mg on day 1, 100 mg on day 2, 200 mg on day 3 and 300 mg on day 4. After day 4, the dose should be titrated to stay between 300-450 mg per day, which is the usual effective dose limits. Depending on the clinical response and patient tolerance, the dose may vary between 150-750 mg per day.

Treatment of moderate to severe episodes of mania in bipolar disorder

In the treatment of moderate to severe manic episodes accompanying bipolar disorder, GYREX® should be taken 2 times a day. The total daily doses to be taken in the first 4 days of treatment are 100 mg on day 1, 200 mg on day 2, 300 mg on day 3 and 400 mg on day 4. For adjustments to increase the dose to 800 mg on day 6, daily increases should not exceed 200 mg.

Depending on the patient's clinical response and tolerance, the dose may vary between 200-800 mg daily. The usual effective dose range is 400 to 800 mg daily.

Treatment of major depressive episodes accompanying bipolar disorder

GYREX® should be taken once a day at bedtime. The total daily doses to be taken in the first 4 days of treatment are 50 mg on day 1, 100 mg on day 2, 200 mg on day 3 and 300 mg on day 4. The recommended daily dose is 300 mg. In clinical studies, no additional benefit was obtained in the 600 mg group compared to the 300 mg group (see section 5.1). 600 mg may be beneficial on an individual basis. In the treatment of bipolar disorder, doses above 300 mg should be started under the supervision of a specialist physician. Clinical studies suggest that if there is concern about tolerance in individual patients, consideration may be given to reducing the dose to a minimum of 200 mg.

Treatment of relapse prevention in bipolar disorder

In the acute treatment of bipolar disorder, patients who have responded to GYREX® should continue to receive the same dose of GYREX® to prevent recurrences of bipolar disorder in manic, mixed or depressive episodes. The dose of GYREX® may vary between 300-800 mg/day twice daily, depending on the clinical response and tolerance of each individual patient. It is important to use the lowest effective dose for maintenance therapy.

Method of administration:

GYREX® is taken orally with or without meals. Tablets taken orally are swallowed with a bit of water.

Additional information on special populations:

Renal failure:

No dose adjustment needed for kidney transplant recipients.

Hepatic failure:

Quetiapine is extensively metabolized in the liver. Therefore, GYREX® should be used with caution in patients with known liver failure, especially during the initial period of treatment. In patients with liver disorders, treatment should be started with 25 mg per day. The dose is then increased daily depending on the clinical response and patient tolerability. It can be increased to the effective dose by increasing it by 25-50 mg.

Pediatric population:

The use of GYREX® in children and adolescents under 18 years of age is not recommended as there is insufficient data to support its use in this age group. Available information from placebo-controlled clinical trials is given in sections 4.4, 4.8, 5.1 and 5.2.

Geriatric population:

Like other antipsychotics, GYREX® should be used with caution in the elderly, especially during the initial dosing period. In elderly patients, GYREX® dose titration may need to be performed more slowly than in younger patients and the daily therapeutic dose may need to be kept lower. The mean plasma clearance of quetiapine in elderly patients is reduced by 30-50% compared to younger patients.

Efficacy and safety in depressive episodes in patients over 65 years of age in the context of bipolar disorder have not been evaluated.

4.3. Contraindications

GYREX® is contraindicated in case of hypersensitivity to the active substance or any of the excipients in its formulation.

Concomitant use of GYREX® with cytochrome P450 3A4 inhibitors such as HIV-protease inhibitors, azole class antifungal drugs, erythromycin, clarithromycin and nefazodone is contraindicated (see section 4.5).

4.4. Special warnings and precautions for use

As GYREX® has many indications, the safety profile should be evaluated depending on the patient's diagnosis and the dose administered.

GYREX® is not approved for the treatment of dementia-related psychosis. Conventional and atypical antipsychotic drugs are associated with an increased risk of death when used in the treatment of elderly patients with dementia-related psychosis.

Pediatric population

The use of antidepressant drugs in children and young people up to the age of 24 may increase suicidal thoughts or behaviors. For this reason, the patient should be closely monitored by both the family and the treating physicians due to unexpected behavioral changes such as restlessness, hyperactivity or the possibility of suicide, especially at the beginning or in the first months of treatment, when the dose of medication is increased/decreased or discontinued.

The use of quetiapine in children and adolescents under 18 years of age is not recommended due to lack of data supporting its use in this age group. Clinical studies with quetiapine have shown side effects in addition to the known safety profile described in adults (see section 4.8); some adverse events (increased appetite, elevated serum prolactin, vomiting, rhinitis and syncope) are more frequent in children and adolescents compared to adults, or different outcomes (extrapyramidal symptoms and irritability) may occur for children and adolescents. For example, an event not previously seen in adults (increased blood pressure) has been described. Changes in thyroid function tests have also been observed in children and adolescents.

In addition, long-term safety results of quetiapine treatment on growth and maturation have not been studied for more than 26 weeks. Long-term results for cognition and behavioral development are not known.

In placebo-controlled clinical trials in children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared with placebo in patients treated for schizophrenia, bipolar mania and bipolar depression (see section 4.8).

Suicidal/ suicidal ideation or clinical deterioration

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

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

Quetiapine may also be associated with an increased risk of suicide-related events when prescribed for other psychiatric conditions. In addition, these conditions may be associated with major depressive episodes. Accordingly, the same precautions should be observed when patients treated for other psychiatric disorders are treated for observed major depressive episodes.

Patients with a history of suicide-related events, who exhibit significant suicidal ideation prior to treatment initiation, are known to be at greater risk of suicidal ideation or suicide attempts and should be carefully monitored throughout treatment. A placebo-controlled meta-analysis in adult patients with psychiatric disorders showed an increased risk of suicidal behavior with antidepressants compared with placebo in patients younger than 25 years.

Patients should be closely monitored following dose changes, especially those at high risk in relation to medication early in treatment. Patients (and caregivers) should be warned that any clinical worsening, suicidal behavior or ideation and unexpected behavioral changes should be monitored and should seek medical advice immediately if these symptoms are present.

In clinical trials in patients with major depressive episodes in bipolar disorder, an increased risk of suicide-related events was observed in young adults under 25 years of age treated with quetiapine compared with those treated with placebo (3% and 0%, respectively).

A retrospective population-based study of quetiapine for the treatment of patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm when quetiapine was used in combination with other antidepressants.

Metabolic risk

Given the risk of worsening of metabolic profiles, including weight, blood glucose (see hyperglycemia) and lipid changes observed in clinical trials, patients' metabolic parameters should be assessed at the start of treatment and changes in these parameters should be checked regularly during the course of treatment. Worsening of these parameters should be managed as clinically appropriate (see section 4.8).

Extrapyramidal symptom

In placebo-controlled clinical trials in adult patients, quetiapine was associated with an increase in extrapyramidal symptoms (EPS) compared to placebo in patients treated with depressive episodes associated with bipolar disorder with quetiapine (see sections 4.8 and 4.8). 5.1).

Quetiapine use has been associated with akathisia, a condition characterized by subjective dissatisfaction or agitated restlessness and the development of a need to move frequently accompanied by an inability to sit or stand. This is likely to occur in the first few weeks of treatment. Increasing the dose may be harmful in patients who develop these symptoms.

Tardive dyskinesia

If signs and symptoms of tardive dyskinesia develop, a dose reduction or discontinuation of quetiapine should be considered. Tardive dyskinesia symptoms may worsen or increase after treatment is discontinued (see section 4.8).

Somnolence and dizziness

Quetiapine treatment has been associated with somnolence and related symptoms such as sedation (see section 4.8). In clinical trials for the treatment of patients with bipolar depression, onset was usually within the first 3 days of treatment and was mostly mild to moderate in intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from the onset of somnolence or until symptoms improve, and discontinuation of treatment may need to be considered.

Orthostatic hypotension

Quetiapine treatment has been associated with orthostatic hypotension and associated dizziness, usually with somnolence beginning during the initial dose adjustment period (see section 4.8). This may increase the incidence of accidental injuries (falls), especially in the elderly patient population. Therefore, patients should be advised to exercise caution when exercising until they become familiar with the potential effects of treatment.

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions that predispose to hypotension. In particular, if orthostatic hypotension occurs in patients with cardiovascular disease, consideration should be given to reducing the dose or making dose titration more gradual.

Sleep apnea syndrome

Sleep apnea syndrome has been reported in patients taking quetiapine. Caution should be exercised when using quetiapine in patients concomitantly taking central nervous system depressants and in overweight/obese or male patients with a history of sleep apnea or at risk of sleep apnea.

Seizures

In controlled clinical trials, there was no difference in seizure incidence between patients given quetiapine or placebo. There are no data on the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended in the treatment of patients with a history of seizures (see section 4.8).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is known to accompany antipsychotic drug treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscle rigidity, autonomic instability and elevated creatine phosphokinase levels. In this case, quetiapine treatment should be stopped and appropriate medical treatment

should be given.

Severe neutropenia and agranulocytosis

Severe neutropenia ($<0.5 \times 10^9/L$) has been reported in clinical trials with quetiapine. Most cases of severe neutropenia developed within a few months after initiation of treatment with quetiapine. There is no apparent relationship with dose. In post-marketing experience, some cases were fatal. Possible risk factors for neutropenia include a pre-existing low leukocyte count (WBC) and a history of drug-induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine treatment should be discontinued in patients with a neutrophil count $<1.0 \times 10^9/L$. However, some cases have occurred in patients without pre-existing risk factors. Patients should be evaluated for signs and symptoms of infection and neutrophil counts should be monitored (until they exceed $1.5 \times 10^9/L$) (see section 5.1).

Neutropenia should be considered in patients presenting with infection or fever, especially in the absence of obvious predisposing factors, and these patients should be managed with close monitoring and emergency care.

Patients should be instructed to report immediately any signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy or sore throat) that may occur at any time during GYREX® treatment. In these patients, especially in the absence of predisposing factors, a leukocyte count and absolute neutrophil count (ANC) should be performed immediately.

Anticholinergic (muscarinic) effects

Norketiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This effect contributes to ADRs reflecting anticholinergic effects when quetiapine is used at recommended doses, in combination with other drugs with anticholinergic effects, and when overdosed. Quetiapine should be used with caution in patients taking medicines with anticholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with currently diagnosed or history of urinary retention, clinically significant prostatic hypertrophy, bowel obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see sections 4.5, 4.8, 5.1 and 4.9).

Interactions

See section 4.5.

The concurrent use of quetiapine with strong hepatic enzyme inducers, such as carbamazepine or phenytoin, leads to significant reductions in quetiapine plasma concentrations, which may affect the effectiveness of quetiapine therapy. In patients receiving hepatic enzyme inducers, quetiapine therapy should only be initiated if the physician considers that the benefits of quetiapine outweigh the risks associated with discontinuing the enzyme inducer. Any change in the inducer should be gradual, and if necessary, it should be replaced with a non-inducing medication (e.g., sodium valproate).

Weight

Weight gain has been reported in patients taking quetiapine. These patients should be monitored and managed clinically appropriately in accordance with the guidelines for antipsychotics used (see sections 4.8 and 5.1).

Hyperglycemia

The development of hyperglycemia and/or exacerbation of pre-existing diabetes during quetiapine treatment has sometimes been associated with ketoacidosis. Coma has rarely been reported, including a few fatal cases (see section 4.8). In some cases, weight gain, which may be a predisposing factor, has been reported. Appropriate clinical monitoring may be recommended according to the antipsychotic guidelines used. Patients treated with any antipsychotic drug, including quetiapine, should be monitored for signs and symptoms of hyperglycemia (polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or patients with risk factors for diabetes mellitus should be regularly monitored for worsening glucose control. Weight should also be monitored regularly.

Lipids

Increases in triglycerides, LDL and total cholesterol levels and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Changes in lipid levels should be treated in accordance with clinical practice.

Prolongation of QT interval

In clinical studies and when used in accordance with the Short Product Information, quetiapine is not associated with sustained prolongation of the absolute QT interval. In postmarketing experience, QT prolongation has been observed at therapeutic doses of quetiapine (see section 4.8) and in overdose (see section 4.9). As with other antipsychotics, quetiapine should be prescribed with caution in patients with cardiovascular disease or a family history of QT prolongation. In addition, caution should be exercised when quetiapine is prescribed with drugs known to prolong the QT interval or in combination with neuroleptics, especially when prescribed to elderly patients with congenital long QT syndrome, congestive heart failure, cardiac hypertrophy, hypokalemia or hypomagnesemia (see section 4.5).

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and postmarketing experience; however, a causal relationship with quetiapine has not been established. Quetiapine treatment should be re-evaluated in patients with suspected cardiomyopathy or myocarditis.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have very rarely been reported with quetiapine treatment, which can be life-threatening or fatal.

SCARs usually occur with one or more of the following symptoms: generalized skin rash that may be itchy or associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Most of these reactions occurred within 4 weeks of starting quetiapine treatment, some DRESS reactions occurred within 6 weeks of starting quetiapine treatment. If signs and symptoms suggestive of these severe skin reactions occur, quetiapine should be discontinued immediately and alternative treatment considered.

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhea, vomiting, drowsiness and hypersensitivity have been described after abrupt discontinuation of quetiapine. It is recommended that treatment is discontinued gradually over a period of at least one to two weeks (see section 4.8).

Elderly patients with dementia-related psychosis

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

In randomized, placebo-controlled, randomized trials of some atypical antipsychotics in patient populations with dementia, the risk of cerebrovascular adverse events increased approximately 3-fold. The mechanism of this increased risk is unknown. The possibility of increased risk cannot be ruled out with other antipsychotics or in other patient populations. Quetiapine should be used with caution in patients with stroke risk factors.

A meta-analysis of atypical antipsychotic drugs reported that atypical antipsychotics are likely to cause an increased risk of death compared to placebo in elderly patients with dementia-related psychosis. However, in two 10-week, placebo-controlled studies using quetiapine in the same patient population (n=710; mean age 83 years, age range 56-99 years), the incidence of mortality was reported to be 5.5% in patients treated with quetiapine and 3.2% in patients given placebo. Patients who participated in these studies died from causes expected in this population.

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

A retrospective population-based study of quetiapine for the treatment of patients with MDD showed an increased risk of death during quetiapine use in patients over 65 years of age. This association was not present when patients with PD were excluded from the analysis. Caution should be exercised if quetiapine is prescribed to elderly patients with PD.

Dysphagia

Dysphagia has been reported with quetiapine (see section 4.8). Quetiapine should be used with caution in patients at risk of aspiration pneumonia.

Constipation and intestinal obstruction

Constipation may represent a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8). These include fatal reports in patients at high risk for intestinal obstruction, including those receiving multiple concomitant therapies leading to reduced intestinal motility and/or constipation symptoms may not be reported. The management of patients with intestinal obstruction/ileus should be closely monitored and emergency care should be provided.

Venous thromboembolism (VTE)

It has been reported that antipsychotic drugs may infrequently cause a risk of venous thromboembolic events (VTE) during their use. Since patients treated with antipsychotics often have risk factors for VTE, all possible risk factors for VTE should be identified and necessary precautions should be taken before and during treatment with quetiapine.

Pancreatitis

Pancreatitis has been reported in clinical trials and during post-marketing experience.

While not all cases could be attributed to risk factors in the post-marketing reports, most patients had factors known to be associated with pancreatitis, including elevated triglyceride levels (see section 4.4), gallstones and alcohol consumption.

Additional information

Data on the use of quetiapine in combination with divalproex or lithium in acute episodes of moderate to severe mania are limited. However, these combination treatments were well tolerated (see sections 4.8 and 5.1). According to the available data, an additive effect occurred at week 3.

Lactose

GYREX® contains 14.13 mg bovine lactose monohydrate in each tablet. Patients with rare inherited galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption problems should not use this medicine.

Misuse and abuse

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

4.5. Interaction with other medicinal products and other forms of interaction

Since quetiapine is a drug that acts primarily on the central nervous system, quetiapine should be used with caution in combination with other drugs that also affect the central nervous system and with alcohol.

Caution should be exercised in the treatment of patients receiving other drugs with anticholinergic (muscarinic) effects (see section 4.4).

Cytochrome P450 (CYP) 3A4 is the major enzyme responsible for the metabolism of quetiapine through the cytochrome P450 enzyme system. In interaction studies in healthy volunteers, the combination of 25 mg quetiapine with ketoconazole, a CYP3A4 inhibitor, resulted in a 5-8-fold increase in quetiapine AUC. Concomitant use of quetiapine with CYP3A4 inhibitors is therefore contraindicated. Quetiapine is also not recommended to be taken with grapefruit juice.

In a multidose study evaluating the pharmacokinetics of quetiapine given before and during treatment with carbamazepine, a known hepatic enzyme inducer, concomitant use with carbamazepine significantly increased quetiapine clearance. With this increase in clearance, the systemic quetiapine effect, as measured by the AUC, decreased to an average of 13% for quetiapine co-administered with carbamazepine compared to normal quetiapine administration, but this decrease was much higher in some patients. As a result of this interaction, quetiapine concentrations in plasma may decrease, which may reduce the effectiveness of quetiapine treatment. Co-administration of quetiapine with phenytoin, another microsomal enzyme inducer, resulted in a very high (450%) increase in quetiapine clearance. Initiation of quetiapine treatment in patients on liver enzyme inducers should only be initiated if the physician considers that the benefits of quetiapine treatment outweigh the risks associated with discontinuation of liver enzyme inducer treatment. Any change in the inducing drug should be gradual and, if necessary, should be replaced by a drug that is not a liver enzyme inducer (e.g. sodium valproate) (see section 4.4).

The pharmacokinetics of quetiapine were not significantly altered when given with the antidepressant imipramine, a known CYP 2D6 inhibitor, or fluoxetine, a known CYP 3A4 and CYP 2D6 inhibitor.

Concomitant administration with risperidone or haloperidol, which are antipsychotics, did not cause significant changes in the pharmacokinetics of quetiapine. Concomitant use of quetiapine and thioridazine increased quetiapine clearance by approximately 70%.

There was no change in the pharmacokinetics of quetiapine following concomitant use with cimetidine.

The pharmacokinetics of lithium did not change when used with quetiapine.

In a 6-week, randomized study of lithium and quetiapine XR versus placebo and quetiapine XR in adult patients with acute mania, the incidence of extrapyramidal-related events (especially tremor), somnolence and weight gain was higher in the lithium group compared to the placebo group (see section 5.1).

The pharmacokinetics of sodium valproate and quetiapine were not altered to clinical significance when used together. In children and adolescents receiving valproate, quetiapine or both together, the incidence of leukopenia and neutropenia was higher in combination groups versus monotherapy groups.

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

Quetiapine should be used with caution in combination with drugs known to cause electrolyte imbalance or prolongation of the QT interval.

False positive results in enzyme immunoassays for methadone and tricyclic antidepressants have been reported in patients receiving quetiapine. It is recommended to confirm suspicious immunoassay screening results with an appropriate chromatographic technique.

Additional information on special populations:

No interaction study has been performed for special populations.

Pediatric population:

No interaction study has been performed for special populations.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C.

Women with childbearing potential / Contraception

There is insufficient information regarding the use of quetiapine and contraception in women of childbearing potential.

Pregnancy

There are insufficient data on the use of quetiapine in pregnant women.

Animal studies have shown reproductive toxicity (see section 5.3). The potential relevance of the

animal findings to humans is unknown.

First trimester

Even in individual reports and some observational studies, published data on pregnancies in which exposure occurred (i.e. 300-1000 pregnancy outcomes), which are not very large, do not suggest a treatment-induced increased risk of malformations. However, no definitive conclusion can be drawn on the basis of the available data. Reproductive toxicity has been observed in animal studies (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the expected benefits clearly outweigh the potential risks.

Third trimester

Newborns exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for abnormal muscle movements (extrapyramidal signs/extrapyramidal symptoms) and/or drug withdrawal symptoms, which may vary in severity following delivery. These symptoms include agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorders. Newborns should therefore be carefully monitored.

Lactation

Based on the very limited data on excretion of quetiapine in human breast milk in published reports, excretion of therapeutic doses of quetiapine into breast milk does not appear to be consistent. In the absence of strong data, it should be decided whether breastfeeding or GYREX® treatment should be discontinued, taking into account the benefit of breastfeeding for the child and the benefit of treatment for the woman.

Fertility

The effects of quetiapine on human fertility have not been studied. Effects due to elevated prolactin levels have been observed in rats; however, these effects are not directly relevant for humans (see section 5.3).

4.7. Effects on ability to drive and use machines

Due to its primary effects on the central nervous system, quetiapine may cause confusion in activities requiring mental alertness. Therefore, patients should be advised not to operate vehicles or machinery until their individual susceptibility to these effects is known.

4.8. Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine ($\geq 10\%$) include somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, increased serum triglyceride levels, elevated total cholesterol (primarily LDL cholesterol), decreased HDL cholesterol, weight gain, reduced hemoglobin, and extrapyramidal symptoms.

Adverse drug reactions associated with quetiapine therapy are listed below by frequency. Frequencies are defined as follows:

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), unknown (cannot be estimated from the available data.)

Blood and lymphatic system disorders

Very common: reduction in hemoglobin²²

Common: Leucopenia^{1,28}, reduction in neutrophil count, increase in eosinophils²⁷

Uncommon: Thrombocytopenia, anemia, reduction in platelet count¹³, neutropenia¹

Rare: Agranulocytosis²⁶

Immune system disorders

Uncommon: Hypersensitivity (including allergic skin reactions)

Very rare: Anaphylactic shock⁵

Endocrine disorders

Common: Hyperprolactinemia¹⁵, decreased total T₄²⁴, decreased free T₄²⁴, decreased total T₃²⁴, increased TSH²⁴

Uncommon: Decreased free T₃²⁴, hypothyroidism²¹

Very rare: Inappropriate antidiuretic hormone secretion.

Metabolism and nutrition disorders

Very common: Increase in serum triglyceride levels^{10,30}, increase in total cholesterol levels^{11,30}, decrease in HDL cholesterol^{17,30}, weight gain^{8,30}

Common: Increased appetite, elevated blood glucose levels (hyperglycemia)^{6,30}

Uncommon: Hyponatremia¹⁹, diabetes mellitus^{1,5}, worsening of pre-existing diabetes

Rare: Metabolic syndrome²⁹

Psychiatric disorders

Common: Abnormal dreams and nightmares, suicidal thoughts, and suicidal behavior.²⁰

Rare: Sleep-related reactions such as sleepwalking, talking in one's sleep, and sleep-related eating disorders.

Nervous system disorders

Very common: Dizziness¹⁶, somnolance², headache, extrapyramidal¹⁶, symptom^{1,21}

Common: Dysarthria

Uncommon: Crisis¹, restless leg Tardive dyskinesia^{1,5}, syncope^{4,16}, confusional state

Eye disorders

Common: Blurred vision

Cardiac disorders

Common: Tachycardia⁴, palpitations²³

Uncommon: QT prolongation^{1,12,18}, bradycardia³²

Unknow: Cardiomyopathy and myocardit

Vascular disorders

Common: Orthostatic hypotension^{4,16}

Rare: Venous thromboembolism¹

Unknow: Stroke³³

Respiratory, thoracic and mediastinal disorders

Common: Dyspnea²³

Uncommon: Rhinitis

Rare: Sleep apnea syndrome

Gastrointestinal disorders

Very common: Dry mouth

Common: Constipation, dyspepsia, vomiting²⁵

Uncommon: Dysphagia⁷

Rare: Pancreatitis¹, intestinal obstruction/ileus

Hepatobiliary disorders

Common: Increase in serum alanine aminotransferase (SAA) levels³, increase in Gamma-GT levels³

Uncommon: Increase in serum aspartate aminotransferase (AST) levels³

Rare: Jaundice⁵, hepatitis

Skin and subcutaneous tissue disorders

Very rare: Angioedema⁵, Stevens-Johnson syndrome⁵

Unknow: Toxic epidermal necrolysis, erythema multiforme, Acute Generalized Exanthematous Pustulosis (AGEP), drug-related rash with eosinophilia and systemic symptoms (DRESS) cutaneous vasculitis

Musculoskeletal, Connective Tissue, and Bone Disorders

Very rare: Rhabdomyolysis

Kidney and urinary tract disorders

Uncommon: Urinary retention

Congenital and hereditary/genetic disorders

Unknow: Neonatal drug withdrawal syndrome³¹

Reproductive system and breast disorders

Uncommon: sexual activity disorders

Rare: Priapism galactorrhea, breast swelling, menstrual irregularities

General disorders and administration site conditions

Very common: Withdrawal (discontinuation) symptoms^{1,9}

Common: Mild asthenia, peripheral edema, irritability, fever

Rare: Neuroleptic malignant syndrome¹, hypothermia

Laboratory Findings

Rare: Increase in serum creatine kinase levels¹⁴

- (1) See section 4.4
- (2) Especially observed during the first two weeks of treatment and generally resolves with discontinuation of quetiapine..
- (3) Asymptomatic increases in serum transaminases (ALT, AST) or gamma-GT levels (increase to $\geq 3X$ ULN at any time) have been observed in some patients receiving quetiapine. These elevations usually resolve during ongoing quetiapine therapy..
- (4) Like other antipsychotics with alpha-1 adrenergic blocker activity, quetiapine can cause blurred vision, tachycardia, and in some patients, syncope and orthostatic hypotension, especially during the initial dose titration period (see Section 4.4).
- (5) The frequency of these adverse drug reactions is based on data from the use of quetiapine film-coated tablets (immediate-release tablets) after their market introduction.
- (6) Measurement of fasting blood glucose ≥ 126 mg/dL (≥ 7 mmol/L) or postprandial blood glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) at least once.
- (7) Increased frequency with quetiapine compared to placebo was observed only in clinical trials for bipolar depression.
- (8) More than 7% increase from baseline is considered. This typically occurs in the initial weeks of treatment.
- (9) Withdrawal symptoms frequently observed in acute placebo-controlled monotherapy trials include insomnia, nausea, headache, diarrhea, vomiting, dizziness, and irritability. The incidence of these reactions significantly decreased one week after discontinuation.
- (10) Measurement of triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) at least once..
- (11) Measurement of cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) at least once. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) is very commonly observed. The average increase in patients is ≥ 41.7 mg/dL (≥ 1.07 mmol/L).
- (12) See the text below.
- (13) Platelets measured as $\leq 100 \times 10^9/L$ at least once.
- (14) Based on clinical trial adverse event reports of blood creatine phosphokinase not being associated with neuroleptic malignant syndrome.
- (15) Prolactin levels at any time (in patients over 18 years of age): >20 $\mu\text{g/L}$ (>869.56 pmol/L) men;
 >30 $\mu\text{g/L}$ (>1304.34 pmol/L) women.
- (16) May cause falls.
- (17) HDL cholesterol at any time: < 40 mg/dL (1,025 mmol/L) in men; < 50 mg/dL (1,282 mmol/L) in women
- (18) Incidence of patients with a deviation in QTC from <450 milliseconds to ≥ 450 milliseconds with an increase of ≥ 30 milliseconds. In placebo-controlled studies with quetiapine, the mean change and the incidence of patients with clinically significant deviations were similar between quetiapine and placebo.
- (19) Transition from > 132 mmol/L to ≤ 132 mmol/L at least once.
- (20) Cases of suicidal ideation and suicidal behavior have been reported during GYREX® quetiapine treatment or in the early period after treatment discontinuation (see sections 4.4 and 5.1).
- (21) See. Section 5.1
- (22) In all studies, including open-label extension, 11% of patients using quetiapine had at least one hemoglobin level < 13 g/dL (8.07 mmol/L) in men and < 12 g/dL (7.45 mmol/L) in women. A decrease to L) has occurred. In these patients, the average maximum decrease in hemoglobin at any time was 1.50 g/dL.
- (23) These reactions often include tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/respiratory disorders.
occurred on the basis of the disease.
- (24) A change from a normal baseline value to a possibly clinically important value at any time after baseline in all studies. Changes in total T4, free T4, total T3, and free T3 were defined as $<0.8 \times \text{LLN}$ (pmol/L) at any time and change in TSH was defined as >5 mIU/L at any time.
- (25) It is based on the increase in the frequency of vomiting in elderly patients (≥ 65 years old).
- (26) From baseline neutrophil count $\geq 0.5 \times 10^9/L$ to $<1.5 \times$ at any time during treatment
Transition to $10^9/L$ (See Section 4.4).
- (27) A shift from a normal baseline value to a possibly clinically important value at any time after baseline in all studies. Changes in eosinophils were defined as $\geq 1 \times 10^9$ cells/L at any time.

(28) A shift from a normal baseline value to a possibly clinically important value at any time after baseline in all studies. Changes in WBCs were defined as $\leq 3 \times 10^9$ cells/L at any time.

(29) Based on reports of metabolic adverse events with quetiapine in all clinical studies.

(30) In clinical studies, some patients experienced multiple metabolic factors including weight, blood glucose and lipids.

More deterioration was observed (See Section 4.4). (31) See. Section 4.6

(32) It occurs at the beginning or during treatment and is associated with hypertension and/or syncope.

Its frequency depends on the bradycardia side effect and related events in clinical studies with quetiapine.

(33) Based on a retrospective, nonrandomized epidemiological study.

QT Prolongation, Ventricular Arrhythmia, Sudden Unexplained Death, Cardiac Arrest, and Torsades de Pointes are reported cases associated with the use of neuroleptics and are considered to be class effects.

Severe Cutaneous Adverse Reactions (SCARs) associated with quetiapine treatment have been reported, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS).

Pediatric Population:

It should be noted that the same adverse drug effects described in adults may also be seen in children and adolescents. The table below summarizes the side effects that are more frequently observed in children and adolescents (aged 10-17) compared to adults, or those that have not been identified in the adult population..

Adverse Drug Effects Associated with Quetiapine in Children and Adolescents that are More Frequent Compared to Adults or Not Described in the Adult Population

Frequencies are defined as:

Very Common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), unknown (cannot be estimated from the available data.)

Endocrine disorders

Very common: Increased prolactin¹

Metabolism and nutrition disorders

Very common: Increased appetite

Neuronal system disorders

Very common: Extrapyramidal Symptoms¹

Common: Syncope

Vascular disorders

Very common: Increased blood pressure²

Respiratory, Chest, and Mediastinal Disorders

Common: Rhinitis

Gastrointestinal Disorders

Very Common: Vomiting

General Disorders and Administration Site Conditions

Common: Irritability²

1. Prolactin levels at any time (patients < 18 years): >20 mcg/L (>869.56 pmol/L) males; >26 mcg/L (>1130.428 pmol/L) girls. Less than 1% of patients have a prolactin level >100 mcg/L has happened.
2. According to groups above clinically significant partners (National Institute of Health) (adapted from Institutes of Health criteria) or > 20 mmHg systolic or Diastolic blood pressure >10 mmHg, two acute (3-6 weeks) placebo-controlled studies administered to children and adolescents.
3. Note: The frequency is that observed in adults, but may be related to different clinical studies, which may be comparable in children and adolescents to adults.
4. See Section 5.1

Reporting of side effects

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Symptoms

Symptoms and signs reported in overdose cases are generally an exaggeration of the drug's known pharmacological effects (drowsiness, sedation, tachycardia, hypotension, and anticholinergic effects). Overdose can lead to QT prolongation, seizures, continuous epilepsy, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma, and death. Patients with a history of severe cardiovascular disease may face an increased risk of overdose effects (see Section 4.4 Orthostatic Hypotension).

Overdose treatment

There is no specific antidote for quetiapine. In cases of severe overdose symptoms, it should be considered that the patient may have taken several different medications simultaneously, and intensive care should be administered. Measures that should be taken include ensuring and maintaining an open airway, providing adequate oxygenation and ventilation, and monitoring and supporting the cardiovascular system.

According to the literature, patients with delirium and agitation, and evident anticholinergic syndrome can be treated with 1-2 mg of physostigmine (under continuous ECG monitoring). Due to potential cardiac conduction side effects of physostigmine, it is not recommended as a standard treatment. Physostigmine may be used if there are no ECG elevations. It should not be used in cases with dysrhythmia, any level of cardiac arrest, or QRS widening.

Prevention of absorption in overdose cases has not been studied. In severe poisoning situations, gastric lavage should be performed, preferably within one hour of ingestion. The administration of activated charcoal should be considered.

In cases of quetiapine overdose, refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Since beta stimulation may worsen hypotension in the context of alpha blockade induced by quetiapine, epinephrine and dopamine should be avoided.

The patient should be kept under close medical supervision and monitored until recovery.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines, tiazepines
ATC code: NO5AH04

Mechanism of action

Quetiapine is an atypical antipsychotic. Quetiapine and its active metabolite, norquetiapine, interact with a variety of neurotransmitter receptors. Both quetiapine and norquetiapine have affinity for serotonin (5HT₂), dopamine D₁, and D₂ receptors in the brain. The higher selectivity of 5HT₂ receptor antagonism compared to D₂ receptors is believed to contribute to quetiapine's clinical antipsychotic properties and its lower incidence of extrapyramidal side effects (EPS) compared to typical antipsychotics. Quetiapine and norquetiapine do not exhibit significant affinity for benzodiazepine receptors; however, they have high affinity for histaminergic and adrenergic alpha₁ receptors, moderate affinity for adrenergic alpha₂ receptors, and intermediate to high affinity for some muscarinic receptors. Norquetiapine's partial agonist effect at 5HT_{1A} sites and NET inhibition may contribute to quetiapine's therapeutic efficacy as an antidepressant.

Pharmacodynamic effect

Quetiapine is active in antipsychotic activity tests, such as avoidance behavior. It blocks the behavioral and electrophysiological effects of dopamine agonists and increases dopamine metabolite concentrations, which are a neurochemical index of D₂ receptor blockade.

In preclinical tests, the prediction of EPS (extrapyramidal symptoms) for quetiapine does not resemble that of typical antipsychotics and shows an atypical profile. At doses that effectively block dopamine D₂ receptors, quetiapine causes only mild catalepsy. Following chronic administration, it provides depolarization blockade, showing selectivity for the limbic system but not for nigrostriatal dopamine-containing neurons. Quetiapine has caused minimal dystonia in Cebus monkeys that were either sensitive to haloperidol or not treated with medication, following both acute and chronic administration (see Section 4.8).

Clinical effect

Schizophrenia

In three placebo-controlled clinical trials using various doses of quetiapine in patients with schizophrenia, there was no difference in the frequency of EPS (extrapyramidal symptoms) or in the concurrent use of anticholinergics between the quetiapine and placebo treatment groups. In a placebo-controlled study, quetiapine doses ranging from 75 to 750 mg/day did not show an increase in EPS or concurrent use of anticholinergics. The long-term efficacy of quetiapine in preventing schizophrenia relapses has not been validated by blinded clinical trials.

In open-label studies, quetiapine was effective in demonstrating clinical improvement in patients with schizophrenia who initially responded to treatment, suggesting long-term efficacy.

Bipolar disorder

In four placebo-controlled clinical trials, quetiapine doses up to 800 mg/day were investigated for the treatment of moderate to severe manic episodes; two of these trials involved monotherapy, and the others involved combination therapy with lithium or divalproex. There was no difference in the frequency of EPS (extrapyramidal symptoms) or in the concurrent use of anticholinergics between the quetiapine and placebo groups.

In the treatment of moderate to severe manic episodes, quetiapine demonstrated superior efficacy compared to placebo in reducing manic symptoms at weeks 3 and 12 in two monotherapy studies. There is no long-term study data demonstrating quetiapine's efficacy in preventing subsequent manic or depressive episodes. Data on quetiapine combined with divalproex or lithium for acute moderate to severe manic episodes are limited to 3 and 6 weeks. However, combination therapy has been well tolerated. Data at 3 weeks showed additive effects, while a second study did not show additive effects at 6 weeks.

In patients who responded to treatment, the average median dose of quetiapine in the final week was approximately 600 mg/day, and about 85% of responders were within the 400 to 800 mg/day dose range.

In four additional clinical studies with quetiapine, patients with bipolar I or bipolar II disorder experiencing moderate to severe depressive episodes were treated with quetiapine at doses of 300 mg and 600 mg over 8 weeks. Compared to patients treated with placebo, quetiapine showed a significant advantage in outcome measures, including average improvement on the MADRS and a response defined as at least a 50% improvement from baseline in the MADRS total score. There was no observed difference in effect intensity between patients receiving the 600 mg dose and those receiving the 300 mg dose.

In the continuation phase of two of these studies, long-term treatment with 300 or 600 mg of quetiapine showed efficacy in reducing depressive symptoms compared to placebo, but not in reducing manic symptoms.

In two relapse prevention studies evaluating the use of quetiapine in combination with mood stabilizers, it was demonstrated that quetiapine combination therapy was superior to mood stabilizer monotherapy in extending the time to the occurrence of any mood episode (manic, mixed, or depressive) in patients with manic, depressive, or mixed mood episodes. Quetiapine was administered in combination with lithium or valproate at a total dose of 400 mg to 800 mg/day, given twice daily.

In a six-week, randomized study involving adult patients with acute mania, the effects of lithium plus quetiapine were compared with those of placebo plus quetiapine. The average improvement difference in the YMRS (Young Mania Rating Scale) between the lithium-added group and the placebo-added group was found to be 2.8, with a 11% difference in the proportion of patients who responded to treatment (defined as at least a 50% improvement in YMRS from baseline) between the two groups (79% in the lithium-added group versus 68% in the placebo-added group).

In a long-term study (up to 2 years) evaluating the prevention of recurrence in patients with

manic, depressive, or mixed mood episodes, quetiapine was found to be superior to placebo in extending the time to the recurrence of any mood episode in patients with bipolar I disorder. The number of patients experiencing a mood episode was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group, and 95 (26.1%) in the lithium group. This result indicated that the transition from quetiapine to lithium did not result in an increase in the time to the recurrence of mood episodes compared to patients who continued on quetiapine.

Clinical studies have shown that, despite quetiapine's half-life being approximately 7 hours, it is effective in treating schizophrenia and mania when administered twice daily. This is also supported by positron emission tomography (PET) studies, which have determined that quetiapine remains active at 5HT₂ and D-receptors for up to 12 hours. Safety and efficacy at doses exceeding 800 mg/day have not been studied.

Clinical safety

In short-term, placebo-controlled clinical trials, the incidence of extrapyramidal symptoms in patients with schizophrenia and bipolar mania was found to be similar between quetiapine and placebo (schizophrenia: 7.8% with quetiapine vs. 8% with placebo; bipolar mania: 11.2% with quetiapine vs. 11.4% with placebo). In short-term, placebo-controlled studies of major depressive disorder (MDD) and bipolar depression, the rate of extrapyramidal symptoms was higher in patients treated with quetiapine compared to placebo. In short-term, placebo-controlled bipolar depression studies, the incidence of extrapyramidal symptoms was 8.9% with quetiapine and 3.8% with placebo. In short-term, placebo-controlled clinical trials for major depressive disorder, the incidence of extrapyramidal symptoms was 5.4% with quetiapine and 3.2% with placebo. In short-term, placebo-controlled studies in elderly patients with major depressive disorder, the incidence of extrapyramidal symptoms was 9% with quetiapine and 2.3% with placebo. In both bipolar depression and MDD, the incidence of adverse events (akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, involuntary muscle contractions, psychomotor hyperactivity, and muscle rigidity) did not exceed 4% in the treatment groups.

In a short-term, fixed-dose (50 mg/day to 800 mg/day) placebo-controlled study (3 to 8 weeks), the average weight gain in patients treated with quetiapine ranged from 0.8 kg with a 50 mg dose to 1.4 kg with a 600 mg dose (lower with 800 mg/day); in the placebo group, it was 0.2 kg. The percentage of patients treated with quetiapine who experienced a weight gain of $\geq 7\%$ of their body weight was 5.3% with the 50 mg/day dose and 15.5% with the 400 mg/day dose (lower with 600 mg and 800 mg/day doses); with placebo, it was 3.7%.

In a six-week, randomized study comparing lithium and quetiapine versus placebo and quetiapine in adults with acute mania, the combination of lithium with quetiapine resulted in a higher incidence of adverse events (63% in the lithium-added group compared to 48% in the placebo-added group). Safety findings revealed that extrapyramidal symptoms developed in 16.8% of patients in the lithium group and 6.6% of patients in the placebo group. The majority of these symptoms were reported as tremor, occurring in 15.6% of the lithium group and 4.9% of the placebo group. The incidence of somnolence was also higher in the lithium-added quetiapine group (12.7%) compared to the placebo-added quetiapine group (5.5%). Additionally, weight gain of $\geq 7\%$ was observed in a greater proportion of patients in the lithium-added group (8%) compared to the placebo group (4.7%).

In long-term relapse prevention studies, there was an open-label phase (4 to 36 weeks) where patients were treated with quetiapine, followed by a randomized withdrawal phase where patients were randomized to either quetiapine or placebo. In patients randomized to quetiapine, the average weight gain during the open-label phase was 2.56 kg; by week 48, the average weight gain during the randomized phase was 3.22 kg compared to the open-label baseline

phase. In patients randomized to placebo, the average weight gain during the open-label phase was 2.39 kg; by week 48, the average weight gain was 0.89 kg compared to the open-label baseline phase.

In placebo-controlled studies involving elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient-years was not higher in the quetiapine group compared to the placebo group.

In all short-term, placebo-controlled monotherapy studies involving patients with baseline neutrophil counts $\geq 1.5 \times 10^9/L$, the rate of experiencing a drop to $< 1.5 \times 10^9/L$ at least once was 1.9% for patients receiving quetiapine and 1.5% for those receiving placebo. The incidence of experiencing a drop in neutrophil count to $> 0.5 - < 1 \times 10^9/L$ was the same for both quetiapine and placebo-treated patients (0.2%). In all clinical studies (placebo-controlled, open-label, active comparator) involving patients with baseline neutrophil counts $\geq 1.5 \times 10^9/L$, the incidence of at least one occurrence of a neutrophil count drop to $< 1.5 \times 10^9/L$ was 2.9% in patients receiving quetiapine, while the same rate for a drop to $< 0.5 \times 10^9/L$ was 0.21%.

Quetiapine treatment has been associated with a dose-dependent decrease in thyroid hormone levels. The incidence of changes in TSH levels was 3.2% in the quetiapine group and 2.7% in the placebo group. In these studies, mutual and potentially clinically significant changes in T3, T4, and TSH levels were rarely observed, and the changes in thyroid hormone levels were not associated with symptomatic hypothyroidism.

The maximum decrease in total and free T4 levels observed during the initial 6 weeks of quetiapine treatment did not persist with long-term therapy. In approximately two-thirds of cases, discontinuation of quetiapine treatment was associated with a reversible effect on total and free T4 levels, regardless of the duration of therapy.

Cataract/ lens blurs

In a long-term clinical study designed to evaluate the cataractogenic potential of risperidone (2-8 mg/day) compared to quetiapine (200-800 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with an increase in lens opacity after at least 21 months of exposure was not higher with quetiapine (4%) compared to risperidone (10%).

Pediatric population

Clinical studies

The efficacy and safety of quetiapine were evaluated in a 3-week placebo-controlled study for the treatment of mania (n=284 patients, USA; ages 10-17). Approximately 45% of the patient population was diagnosed with ADHD. Additionally, a 6-week placebo-controlled schizophrenia treatment study was conducted (n=222, ages 13-17). In both studies, patients known not to respond to quetiapine were excluded. Treatment with quetiapine was started at a dose of 50 mg/day and increased to 100 mg/day on the second day. The dose was then titrated to the target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day); the dose was increased by 100 mg/day twice or three times daily.

In the mania study, the average change in the YMRS (Young Mania Rating Scale) total score compared to baseline was -5.21 for 400 mg/day quetiapine and -6.56 for 600 mg/day quetiapine. Response rates (YMRS improvement $\geq 50\%$) were 64% for quetiapine 400 mg/day, 58% for quetiapine 600 mg/day, and 37% for the placebo group.

In the schizophrenia study, the average change in the PANSS (Positive and Negative Syndrome Scale) total score compared to baseline was -8.16 for 400 mg/day quetiapine and -9.29 for 800 mg/day quetiapine. Neither the low dose (400 mg/day) nor the high dose (800 mg/day) quetiapine regimen was superior to placebo in terms of the percentage of patients achieving a $\geq 30\%$ reduction in the PANSS total score compared to baseline. In both mania and schizophrenia, higher doses resulted in numerically lower response rates.

In three short-term placebo-controlled monotherapy studies, quetiapine was not effective in children and adolescents (ages 10-17) with bipolar depression.

There is no data available regarding the maintenance of efficacy or prevention of recurrence in this age group.

Clinical Safety

In the aforementioned short-term pediatric quetiapine studies, the incidence of EPS (extrapyramidal symptoms) in the active treatment group compared to placebo was 12.9% versus 5.3% in the schizophrenia study; 3.6% versus 1.1% in the bipolar mania study; and 1.1% versus 0% in the bipolar depression study. The percentage of patients experiencing a $\geq 7\%$ increase in body weight compared to baseline in the active treatment group was 17% versus 2.5% in the schizophrenia and bipolar studies, and 13.7% versus 6.8% in the bipolar depression study. The incidence of suicide-related events in the active treatment group compared to placebo was 1.4% versus 1.3% in the schizophrenia study; 1% versus 0% in the bipolar mania study; and 1.1% versus 0% in the bipolar depression study. During the post-treatment extension follow-up phase of the bipolar depression study, two additional suicide-related events were observed in two patients; one of these patients was receiving quetiapine at the time of the events.

Long Term Safety

In 26-week open-label extension phases of acute studies (n=380), quetiapine administered in a flexible dose range of 400-800 mg/day provided additional safety data. In children and adolescents, increases in blood pressure and appetite were reported; compared to adults, extrapyramidal symptoms and increases in serum prolactin levels were observed more frequently in children and adolescents (see Sections 4.4 and 4.8). Regarding weight gain, when evaluated in the context of normal growth over the long term, a change of at least 0.5 standard deviations in the baseline body mass index (BMI) was used as a criterion for clinically significant change; 18.3% of patients treated with quetiapine for at least 26 weeks met this criterion.

5.2. Pharmacokinetics properties

General properties

Absorption:

Quetiapine is well absorbed following oral administration and is extensively metabolized. The bioavailability of quetiapine is not significantly affected when taken with food. The steady-state peak plasma concentrations of the active metabolite norquetiapine are approximately 35% of those observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear within the approved dose range.

Distribution:

Quetiapine is 83% bound to plasma proteins.

Biotransformation:

Quetiapine is extensively metabolized in the liver, and less than 5% of the unchanged parent compound is excreted in the urine or feces following the administration of radiolabeled quetiapine.

It has been demonstrated in in vitro studies that the main enzyme responsible for the metabolism of quetiapine via cytochrome P450 is CYP3A4. The formation and elimination of norquetiapine is primarily mediated by the CYP3A4 enzyme.

Approximately 73% of the radioactivity is excreted in the urine, and 21% is excreted in the feces.

It has been demonstrated in vitro that quetiapine and several of its metabolites are weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6, and 3A4 activities. In humans, in vitro CYP inhibition only occurs at plasma concentrations 5 to 50 times higher than those associated with quetiapine doses ranging from 300 to 800 mg per day. Based on these in vitro results, it is unlikely that quetiapine will significantly inhibit the metabolism of other drugs metabolized through the cytochrome P450 system when used in combination with other medications. Studies in animals have suggested that quetiapine might induce cytochrome P450 enzymes. However, in a specific interaction study conducted with psychotic patients, no increase in cytochrome P450 activity was observed following quetiapine administration.

Elimination:

The elimination half-lives of quetiapine and its active metabolite, norquetiapine, are 7 and 12 hours, respectively. Less than 5% of the average molar dose fraction of free quetiapine and norquetiapine in human plasma is excreted via the urine.

Linearity/Non-Linearity:

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional at doses up to 800 mg administered once daily.

Characteristics of patients

Gender:

There is no difference in the pharmacokinetics of quetiapine between men and women

Geriatric population:

In elderly individuals, the average clearance of quetiapine has decreased by approximately 30% to 50% compared to adults aged 18 to 65 years.

Renal failure:

The average plasma clearance of quetiapine in patients with severe renal impairment (creatinine clearance <30 mL/min/1.73 m²) has decreased by approximately 25%. However, individual clearance values remain within the range observed in normal individuals.

Liver failures:

In patients with known liver failures (stable alcoholic cirrhosis), the average plasma clearance of quetiapine has decreased by approximately 25%. Given that quetiapine is extensively metabolized by the liver, an increase in plasma levels is anticipated in individuals with liver dysfunction. Dose adjustment may be necessary for this patient group (see Section 4.2).

Pediatric population:

Pharmacokinetic data were obtained from 9 children (ages 10-12) and 12 adolescents (ages 13-17) treated with 400 mg of quetiapine (GYREX®) twice daily at steady state. Plasma levels of the parent compound quetiapine at steady state were similar in children and adolescents (ages 10-17) to those in adults; however, in children, the C_{max} value was at the higher end of the range observed in adults. Compared to adults, the active metabolite norquetiapine had higher AUC and C_{max} values in children (ages 10-12) by 62% and 49%, respectively; in adolescents (ages 13-17), these values were higher by 28% and 14%, respectively.

5.3. Preclinical safety data

In vitro and *in vivo* studies did not show any evidence of genotoxicity. Deviations were observed in laboratory animals following clinically relevant doses, but these were not confirmed by long-term clinical trials.

In rats, pigmentation of the thyroid gland was observed. In cynomolgus monkeys, there was thyroid follicular cell hypertrophy, a decrease in T3 levels, and a reduction in hemoglobin concentration with a decrease in both red and white blood cell counts. In dogs, lens opacity and cataracts were observed (see Section 5.1. Cataracts/Lens Opacities).

In rabbits, an embryofetal toxicity study showed an increased incidence of carpal/tarsal flexure in the fetus. This effect was observed in the presence of apparent maternal effects such as decreased body weight gain. These effects were seen at maternal exposure levels similar to or slightly above the maximum therapeutic dose in humans. The relevance of this finding to humans is unknown.

In a fertility study in rats, marginal decreases in male fertility, pseudopregnancy, prolonged diestrus periods, prolonged pre-coital intervals, and reduced pregnancy rates were observed. These effects are associated with elevated prolactin levels and are not directly relevant to humans due to differences in hormonal reproductive control between species.

6. PHARMACEUTICAL PROPERTIES

6.1. List of Excipients

Polyvinylpyrrolidone
Calcium hydrogen phosphate dihydrate
Microcrystalline cellulose
Sodium starch glycolate
Lactose monohydrate (bovine source)
Magnesium stearate
Hydroxypropyl methylcellulose
Titanium dioxide
Talc
Polyethylene glycol
Yellow Iron Oxide

6.2. Incompatibilities

Unknown.

6.3. Shelf-life

48 months

6.4. Special precautions for storage

Keep at room temperature below 25°C an in original package.

6.5. Nature and contents of container

30 and 60 film-coated tablets, provided in blister packs.

6.6. Special precautions for disposal of waste materials derived from the medicinal product and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORIZATION HOLDER

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Halide Edip Adivar Mahallesi, Boruçiçeği Sok. No:16
34382 Şişli – İSTANBUL
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8. MARKETING AUTHORIZATION NUMBER(S)

212/54

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Initial authorization date: 31.08.2007

Dare of authorization: 29.04.2014

10. DATE OF RENEWAL OF SmPC