

 **10 October 2024**

**SUMMARY OF PRODUCT CHARACTERISTICS**

**for**

**Quetiapin "Lannacher", film-coated tablets**

**0. D.SP.NO.**

24784

**1. NAME OF THE MEDICINAL PRODUCT**

Quetiapin "Lannacher"

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

*Quetiapin "Lannacher" 25 mg film-coated tablets:*

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

*Excipients with known effect:*

One tablet contains 1 mg of lactose monohydrate and 0.07 mg lecithin (soya) (see section 4.4).

*Quetiapin "Lannacher" 100 mg film-coated tablets:*

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

*Excipients with known effect:*

One tablet contains 4 mg of lactose monohydrate and 0.21 mg lecithin (soya) (see section 4.4).

*Quetiapin "Lannacher" 200 mg film-coated tablets:*

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

*Excipients with known effect:*

One tablet contains 8 mg of lactose monohydrate and 0.42 mg lecithin (soya) (see section 4.4).

*Quetiapin "Lannacher" 300 mg film-coated tablets:*

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

*Excipients with known effect:*

One tablet contains 12 mg of lactose monohydrate and 0.63 mg lecithin (soya) (see section 4.4).

For the full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film-coated tablets

*Quetiapin "Lannacher" 25 mg film-coated tablets:*

Peach coloured, round, biconvex film coated tablets.

*Quetiapin "Lannacher" 100 mg film-coated tablets:*

Yellow coloured, round, biconvex film-coated tablets with a score line on one side\*

*Quetiapin "Lannacher" 200 mg film-coated tablets:*

White, round, biconvex film-coated tablets.

*Quetiapin "Lannacher" 300 mg film-coated tablets:*

White, capsule shaped, film-coated tablets with a score line on one side\*

\* The tablet can be divided into equal doses.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Quetiapin "Lannacher" is indicated for

* treatment of schizophrenia
* treatment of bipolar disorder:
* for the treatment of moderate to severe manic episodes in bipolar disorder
* for the treatment of major depressive episodes in bipolar disorder
* for the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.

**4.2 Posology and method of administration**

Posology

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.

*Adults*

*For the treatment of schizophrenia*

For the treatment of schizophrenia Quetiapin "Lannacher" should be administered twice a day. The total daily dose for the first four 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 usual effective dose of 300 to 450 mg per day.

Depending on the clinical response and tolerability of the individual patient, the dose may be adjusted within the range 150 to 750 mg per day.

*For the treatment of moderate to severe manic episodes in bipolar disorder*

For the treatment of manic episodes associated with bipolar disorder, Quetiapin "Lannacher" should be administered twice a day. The total daily dose for the first four 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 per day by Day 6 should be in increments of no greater than 200 mg per day.

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

*For the treatment of major depressive episodes in bipolar disorder*

Quetiapin "Lannacher" should be administered once daily at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

*For preventing recurrence in bipolar disorder*

For prevention or recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to quetiapine for acute treatment of bipolar disorder should continue therapy at the same dose. The dose may be adjusted depending on clinical response and tolerability of the individual patient, within the range of 300 to 800 mg/day administered twice daily. It is important that the lowest effective dose is used for maintenance therapy.

*Elderly*

As with other antipsychotics, Quetiapin "Lannacher" should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than those used in younger patients, depending on the clinical response and tolerability of the individual patient. The mean plasma clearance of quetiapine was reduced by 30 to 50 % in elderly subjects when compared to younger patients.

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

*Paediatric population*

Quetiapin "Lannacher" 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. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

*Renal impairment*

Dosage adjustment is not necessary in patients with renal impairment.

*Hepatic impairment*

Quetiapine is extensively metabolised by the liver. Therefore, Quetiapin "Lannacher" should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Dosing in patients with known hepatic impairment should begin with 25 mg/day. The dosage should be increased daily with increments of 25 to 50 mg/day until an effective dosage is reached, depending on the clinical response and tolerability of the individual patient.

Method of administration

Oral use.

Quetiapin "Lannacher" can be administered with or without food.

**4.3 Contraindications**

* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
* Hypersensitivity to peanut or soya (see section 4.4)
* Concomitant administration of cytochrome P450 3A4-inhibitors, such as HIV-protease inhibitors, azole-antifungals, erythromycin, clarithromycin and nefazodone, is contraindicated (see section 4.5).

**4.4 Special warnings and precautions for use**

As quetiapine has several indications, the safety profile should be considered with respect to the individual patient’s diagnosis and the dose being administered.

**Paediatric population**

Quetiapin "Lannacher" 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. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults (see section 4.8), 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.

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

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

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions when treating patients with major depressive episodes should therefore be taken when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta-analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

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

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine compared to those treated with placebo (3.0 % vs. 0 %, respectively).

**Metabolic risk**

Given the risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was observed in clinical studies, the metabolic parameters of the patient should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled during the course of the treatment. Worsening in these parameters should be managed as clinically appropriate (see also section 4.8).

**Extrapyramidal symptoms**

In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder (see sections 4.8 and 5.1).

The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and the 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. Increasing the dose may be detrimental in patients who develop these symptoms.

**Tardive dyskinesia**

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (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 predominantly of mild to moderate 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 treatment discontinuation may need to be considered.

**Orthostatic hypotension**

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see section 4.8) which, like somnolence, has its onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Quetiapin "Lannacher" 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 of sleep apnoea, such as patients who are overweight/obese or male, quetiapine should be used with caution.

**Seizures**

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, 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 antipsychotic treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

**Serotonin syndrome**

Concomitant administration of Quetiapin "Lannacher" and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (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 neutropenia (neutrophil count < 0.5 x 109/l) has been reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months after starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count < 1.0 x 109/l. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5 x 109/l) (see section 5.1).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g., fever, weakness, lethargy, or sore throat) at any time during Quetiapin "Lannacher" therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

**Anti-cholinergic (muscarinic) effects:**

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications with anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications with anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see sections 4.5, 4.8, 4.9 and 5.1).

**Interactions**

See also section 4.5.

Concomitant use of quetiapine with strong hepatic enzyme inducers such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy.

In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

**Weight**

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate in accordance with utilised antipsychotic guidelines (see sections 4.8 and 5.1).

**Hyperglycaemia**

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma have been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness), and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

**Lipids**

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

**QT prolongation**

In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing experience, QT prolongation was reported with quetiapine at therapeutic doses (see section 4.8) and in overdose (see section 4.9). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Further, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5).

**Cardiomyopathy and myocarditis**

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience (see section 4.8). In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.

**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) which can be life-threatening or fatal have been reported very rarely with quetiapine treatment. 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. Most of these reactions occurred within 4 weeks after initiation of quetiapine therapy, some DRESS reactions occurred within 6 weeks after initiation of quetiapine therapy. If signs and symptoms suggestive of these severe skin reactions appear, quetiapine should be withdrawn immediately and alternative treatment should be considered.

**Withdrawal**

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see section 4.8).

**Elderly patients with dementia-related psychosis**

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

An approximately 3-fold increased risk of cerebrovascular adverse events has been observed in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotic drugs, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo.

However in two, 10-week placebo-controlled quetiapine studies in the same patient population (n = 710; mean age: 83 years; range: 56 to 99 years) the incidence of mortality in quetiapine-treated patients was 5.5 % versus 3.2 % in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population.

**Elderly patients with Parkinson’s disease (PD)/parkinsonism**

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

**Dysphagia**

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

**Constipation and intestinal obstruction**

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

**Venous thromboembolism (VTE)**

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

**Pancreatitis**

Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients exhibited factors known to be associated with pancreatitis such as increased triglycerides (see section 4.4), gallstones, and alcohol consumption.

**Additional information**

Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see sections 4.8 and 5.1). The data showed an additive effect at week 3.

**Misuse and abuse**

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

**Lactose**

Quetiapin "Lannacher" contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Lecithin**

Quetiapin "Lannacher" contains lecithin derived from soya and may contain soya protein. Consequently, lecithin (soya) may be allergenic for patients who are hypersensitive to soya.

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

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

Quetiapine should be used with caution in combination with serotonergic medicinal products, 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).

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

Cytochrome P 450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers the concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor caused a five- to eight-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

In a multiple dose trial in patients assessing 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. Because of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine with phenytoin (another microsomal enzyme inducer) caused an increase in the clearance of quetiapine of approximately 450 %. In patients, receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual and, if required, replaced by a non-inducer (e.g. sodium valproate) (see section 4.4).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antidepressants imipramine (a known CYP2D6 inhibitor) or fluoxetine (a known CYP3A4 and CYP2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered following co-administration with the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increase in the clearance of quetiapine of approximately 70 %.

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

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

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

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study in children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

Formal interaction studies with commonly used cardiovascular drugs have not been performed.

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

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

*First trimester*

The moderate amount of published data from exposed pregnancies (i.e. between 300 to 1,000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to quetiapine treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

*Third trimester*

Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding

Based on very limited data from published reports, excretion of quetiapine into human breast milk at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Quetiapin "Lannacher" therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were observed in rats, although these data are not directly relevant for humans (see section 5.3).

**4.7 Effects on ability to drive and use machines**

No traffic warning.

Given the primary central nervous system effects, quetiapine 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 common reported Adverse Drug Reactions (ADRs) with quetiapine (≥ 10 %) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

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

The incidences of ADRs associated with quetiapine therapy, are listed below according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group; 1995).

The following frequency estimates are used in assessing undesirable effects:

Very common: (≥ 1/10)

Common: (≥ 1/100 to < 1/10)

Uncommon: (≥ 1/1,000 to < 1/100)

Rare: (≥ 1/10,000 to < 1/1,000)

Very rare: (< 1/10,000)

Not known: (cannot be estimated from the available data)

*Blood and lymphatic system disorders*

*Very common:* Decreased haemoglobin22

*Common:* Leucopenia1,28, decreased neutrophil count, eosinophils increased27

*Uncommon:* Thrombocytopenia, anaemia, platelet count decreased13, Neutropenia1

*Rare:* Agranulocytosis26

*Immune system disorders*

*Uncommon:* Hypersensitivity (including allergic skin reactions)

*Very rare:* Anaphylactic reaction5

*Endocrine disorders*

*Common:* Hyperprolactinaemia15, decreases in total T424, decreases in free T424, decreases in total T324, increases in TSH24

*Uncommon:* Decreases in free T324, hypothyroidism21

*Very rare:* Inappropriate antidiuretic hormone secretion

*Metabolism and nutrition disorders*

*Very common:* Elevations in serum triglyceride levels10,30, elevations in total cholesterol (predominantly LDL cholesterol)11,30, decreases in HDL cholesterol17,30, weight gain8,30

*Common:* Increased appetite, blood glucose increased to hyperglycaemic levels6, 30

*Uncommon:* Hyponatraemia19, diabetes mellitus1,5, exacerbation of pre-existing diabetes

*Rare:* Metabolic syndrome29

*Psychiatric disorders*

*Common:* Abnormal dreams and nightmares, suicidal ideation and suicidal behaviour20

*Rare:* Somnambulism and related reactions such as sleep talking and sleep related eating disorder

*Nervous system disorders*

*Very common:* Dizziness4,16, somnolence2,16, headache, extrapyramidal symptoms1, 21

*Common:* Dysarthria

*Uncommon:* Seizure1, restless-legs-syndrome, tardive dyskinesia1,5, syncope4,16, confusional state

*Eye disorders*

*Common:* Vision blurred

*Cardiac disorders*

*Common:* Tachycardia4, palpitations23

*Uncommon:* Bradycardia32, QT prolongation1,12, 18

*Not known:* Cardiomyopathy, myocarditis

*Vascular disorders*

*Common:* Orthostatic hypotension4,16

*Rare:* Venous thromboembolism1

*Not known:* Stroke33

*Respiratory, thoracic and mediastinal disorders*

*Common:* Dyspnoea23

*Uncommon:* Rhinitis

*Gastrointestinal disorders*

*Very common:* Dry mouth

*Common:* Constipation, dyspepsia, vomiting25

*Uncommon:* Dysphagia7

*Rare:* Pancreatitis1, intestinal obstruction/ileus

*Hepatobiliary disorders*

*Common:* Elevations in serum alanine aminotransferase (ALT)3, elevations in gamma-GT levels3

*Uncommon:* Elevations in serum aspartate aminotransferase (AST)3

*Rare:* Jaundice5, hepatitis

*Skin and subcutaneous tissue disorders*

*Very rare:* Angiooedema5, Stevens-Johnson syndrome5

*Not known:* Toxic epidermal necrolysis, erythema multiforme, acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), cutaneous vasculitis

*Musculoskeletal and connective tissue disorders*

*Very rare:* Rhabdomyolysis

*Renal and urinary disorders*

*Uncommon:* Urinary retention

*Pregnancy, puerperium and perinatal conditions*

*Not known:* Drug withdrawal syndrome neonatal31

*Reproductive system and breast disorders*

*Uncommon:* Sexual dysfunction

*Rare:* Priapism, galactorrhoea, breast swelling, menstrual disorder

*General disorders and administration site conditions*

*Very common:* Withdrawal (discontinuation) symptoms1,9

*Common:* Mild asthenia, peripheral oedema, irritability, pyrexia

*Rare:* Neuroleptic malignant syndrome1, hypothermia

*Investigations*

*Rare:* Elevations in blood creatine phosphokinase14

1. See section 4.4.
2. Somnolence may occur, usually during the first two weeks of treatment, and generally resolves with continued administration of quetiapine.
3. Asymptomatic elevations (shift from normal to > 3 x ULN at any time) in serum transaminases (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.
4. As with other antipsychotics with α-1-adrenergic-blocking activity, quetiapine may commonly induce orthostatic hypotension, associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period (see section 4.4).
5. Calculation of frequencies for these ADRs has only been taken from postmarketing data.
6. Fasting blood glucose ≥ 126 mg/dl (≥ 7.0 mmol/l) or a non-fasting blood glucose ≥ 200 mg/dl (≥ 11.1 mmol/l)on at least one occasion.
7. An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.
8. Based on > 7 % increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.
9. The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.
10. Triglycerides ≥ 200 mg/dl (≥ 2.258 mmol/l) (patients ≥ 18 years of age) or ≥ 150 mg/dl (1.694 mmol/l) (patients < 18 years of age) on at least one occasion.
11. Cholesterol ≥ 240 mg/dl (≥ 6.2064 mmol/l) (patients ≥ 18 years of age) or ≥ 200 mg/dl (5.172 mmol/l) (patients < 18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dl (≥ 0.769) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dl (≥ 1.07 mmol/l).
12. See text below.
13. Platelets ≤100 x 109/l on at least one occasion.
14. Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.
15. Prolactin levels (patients > 18 years of age) > 20 μg/l (> 869.56 pmol/l) males, > 30 μg/l (> 1304.34 pmol/l) females at any time.
16. May lead to falls.
17. HDL cholesterol: < 40 mg/dl (1.025 mmol/l) males; < 50 mg/dl (1.282 mmol/l) females at any time.
18. Incidence of patients who have a QTc shift from < 450 msec to ≥ 450 msec with a ≥ 30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.(19) Shift from > 132 mmol/l to < 132 mmol/l on at least one occasion.
19. Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see sections 4.4 and 5.1).
20. See section 5.1.
21. Decreased haemoglobin to ≤ 13 g/dl (8.07 mmol/l) males, ≤ 12 g/dl (7.45 mmol/l) females on at least one occasion occurred in 11 % of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in hemoglobin at any time was -1.50 g/dl.
22. These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension, and/or underlying cardiac/respiratory disease.
23. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in total T4, free T4, total T3 and free T3 are defined as < 0.8 x LLN (pmol/l) and shift in TSH is > 5 mIU/l at any time.
24. Based upon the increased rate of vomiting in elderly patients (≥ 65 years of age).
25. Based on shift in neutrophils from ≥ 1.5 x 109/l at baseline to < 0.5 x 109/l at any time during treatment and based on patients with severe neutropenia (< 0.5 x 109/l) and infection during all quetiapine clinical trials (see section 4.4).
26. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as > 1 x 109 cells/l at any time.
27. Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x 109 cells/l at any time.
28. Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.
29. In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see section 4.4).
30. See section 4.6.
31. May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.
32. Based on one retrospective non-randomised epidemiologic study.

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

**Paediatric population**

The same ADRs described above for adults should be considered for children and adolescents. The following summarises ADRs that occur at a higher frequency in children and adolescent patients (10 to 17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

The frequencies of adverse events are ranked according to the following: Very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1/1,000) and very rare (< 1/10,000).

*Endocrine disorders*

*Very common:* Elevations in prolactin1

*Metabolism and nutritional disorders*

*Very common:* Increased appetite

*Nervous system disorders*

*Very common:* Extrapyramidal symptoms3, 4

*Common:* Syncope

*Vascular disorders*

*Very common:* Increases in blood pressure2

*Respiratory, thoracic and mediastinal disorders*

*Common:* Rhinitis

*Gastrointestinal disorders*

*Very common:* Vomiting

*General disorders and administration site conditions*

*Common:* Irritability3

1. Prolactin levels (patients < 18 years of age): > 20 μg/l (> 869.56 pmol/l) males; > 26 μg/l (> 1130.428 pmol/l) females at any time. Less than 1 % of patients had an increase to a prolactin level > 100 μg/l.
2. Based on shifts above clinically significant thresholds (adapted from the National Institute of Health criteria) or increases > 20 mmHg for systolic or > 10 mmHg for diastolic blood pressure at any time in two acute (3 to 6 weeks) placebo-controlled trials in children and adolescents.
3. Note: the frequency is consistent to that observed in adults, but irritability might be associated with different clinical implications in children and adolescents as compared to adults.
4. See section 5.1.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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:

Lægemiddelstyrelsen

Axel Heides Gade 1

DK-2300 København S

Website: www.meldenbivirkning.dk

**4.9 Overdose**

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance’s known pharmacological effects, i.e. drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects.

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death.

Patients with preexisting severe cardiovascular disease may be at an increased risk of the effects of overdose (see section 4.4).

Management of overdose

There is no specific antidote for quetiapine. 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 anticholinergic syndrome may be treated with physostigmine, 1 to 2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, due to the 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, should be performed 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. 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.

**4.10 Legal status**

 B

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Diazepines, oxazepines, and thiazepines, ATC-code: N05AH04.

Mechanism of action

Quetiapine is an atypical antipsychotic agent.

Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5-HT2) and dopamine D1 and D2 receptors. This combination of receptor antagonism with a higher selectivity for serotonin 5-HT2 relative to D2 receptors is believed to contribute to the clinical antipsychotic properties and low extrapyramidal symptom (EPS) liability of quetiapine compared to typical antispychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptors, which may explain anti-cholinergic (muscarinic) effects. Inhibition of NET and partial agonist action at 5-HT1A sites by norquetiapine may contribute to Quetiapin "Lannacher"’s therapeutic efficacy as an antidepressant.

Pharmacodynamic effects

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and it elevates dopamine metabolite concentrations, a neurochemical index of D2 receptor blockade.

In preclinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D2 receptor supersensitivity after chronic administration. It produces only weak catalepsy at effective dopamine D2 receptor-blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naïve Cebus monkeys after acute and chronic administration (see section 4.8).

Clinical efficacy

*Schizophrenia*

In three placebo-controlled clinical trials, in patients with schizophrenia, using variable doses of quetiapine, there were no differences between the quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anticholinergics. A placebo-controlled trial evaluating fixed doses of quetiapine across the range of 75 to 750 mg/day showed no evidence of an increase in EPS or the use of concomitant anticholinergics. The long-term efficacy of quetiapine IR in prevention of schizophrenic relapses has not been verified in blinded clinical trials. In open label trials in patients with schizophrenia, quetiapine was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response, suggesting some long-term efficacy.

*Bipolar disorder*

In four placebo-controlled clinical trials evaluating doses of quetiapine up to 800 mg/day for the treatment of moderate to severe manic episodes, two each in monotherapy and as combination therapy to lithium or divalproex, there were no differences between the quetiapine and placebo treatment groups in the incidence of EPS or concomitant use of anti-cholinergics.

In the treatment of moderate to severe manic episodes, quetiapine demonstrated superior efficacy compared to placebo in reduction of manic symptoms at 3 and 12 weeks, in two mono­therapy trials. There are no data from long-term studies to demonstrate quetiapine’s effectiveness in preventing subsequent manic or depressive episodes. Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

The mean last week median dose of quetiapine in responders was approximately 600 mg/day and approximately 85 % of the responders were in the dose range of 400 to 800 mg per day.

In four clinical trials with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, quetiapine IR 300 mg and 600 mg was significantly superior compared to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50 % improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg quetiapine IR and those who received 600 mg.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on quetiapine IR 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating quetiapine in combination with mood stabilizers in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior compared to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine was administered twice-daily totaling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In a 6-week, randomised, study of lithium and quetiapine XR versus placebo and quetiapine XR in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50 % improvement from baseline on the YMRS) was 11 % (79 % in the lithium add-on group vs. 68 % in the placebo add-on group).

In one long-term study (up to 2 years of treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior compared to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups, respectively. The results indicated that in patients who responded to quetiapine, a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event, when comparing continuous quetiapine treatment with a switch from quetiapine to lithium treatment.

Clinical trials have demonstrated that quetiapine is effective in schizophrenia and mania when given twice a day, although quetiapine has a pharmacokinetic half-life of approximately 7 hours. This is further supported by the data from a positron emission tomography (PET) study, which showed that 5-HT2- and D2-receptor occupancy is maintained for up to 12 hours for quetiapine. The safety and efficacy of doses greater than 800 mg/day have not been evaluated.

Clinical safety

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8 % for quetiapine and 8.0 % for placebo; bipolar mania: 11.2 % for quetiapine and 11.4 % for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials, the aggregated incidence of extrapyramidal symptoms was 8.9 % for quetiapine compared to 3.8 % for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4 % for quetiapine XR and 3.2 % for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0 % for quetiapine XR and 2.3 % for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (e.g., akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4 % in any treatment group.

In short term, fixed dose (50 mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain of quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg of placebo treated patients. The percentage of quetiapine treated patients who gained ≥7 % of body weight ranged from 5.3 % for the 50 mg daily dose to 15.5 % for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7 % for placebo treated patients.

A 6-week, randomised, study of lithium and quetiapine XR versus placebo and quetiapine XR in adult patients with acute mania indicated that the combination of quetiapine XR with lithium leads to more adverse events (63 % versus 48 % in patients treated with quetiapine XR in combination with placebo). The safety results showed a higher incidence of extrapyramidal symptoms reported in 16.8 % of patients in the lithium add-on group and 6.6 % in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6 % of the patients in the lithium add-on group and 4.9 % in the placebo add-on group. The incidence of somnolence was higher in the lithium add-on group (12.7 %) compared to the placebo add-on group (5.5 %). In addition, a higher percentage of patients in the lithium add-on group (8.0 %) had gained weight (≥ 7 %) at the end of treatment compared to patients in the placebo add-on group (4.7 %).

Longer-term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomized withdrawal period during which patients were randomized to quetiapine or placebo. For patients who were randomized to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomized period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomized to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomized period the mean weight gain was 0.89 kg, compared to open label baseline.

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

In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥ 1.5 x 109/l, the incidence of at least one occurrence of a shift to neutrophil count < 1.5 x 109/l, was 1.9 % in patients treated with quetiapine compared to 1.5 % in placebo-treated patients. The incidence of shifts to > 0.5 to < 1.0 x 109/l was the same (0.2 %) in patients treated with quetiapine and placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥ 1.5 x 109/l, the incidence of at least one occurrence of a shift to neutrophil count < 1.5 x 109/l was 2.9 % and to < 0.5 x 109/l was 0.21 % in patients treated with quetiapine.

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism.

The reduction in total and free T 4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment.

*Cataracts/lens opacities*

In a clinical trial to evaluate the cataractogenic potential of quetiapine (200 to 800 mg/day) versus risperidone (2 to 8 mg) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in quetiapine (4 %) compared with the risperidone group (10 %), for patients with at least 21 months of exposure.

Paediatric population

Clinical efficacy

The efficacy and safety of quetiapine was studied in a 3-week placebo controlled study for the treatment of mania (n = 284 patients from the US, aged 10 to 17). About 45 % of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n = 222 patients, aged 13 to 17) was performed. In both studies, patients with a known lack of response to quetiapine were excluded. Treatment with quetiapine was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400 to 600 mg/day; schizophrenia 400 to 800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was –5.21 for quetiapine 400 mg/day and –6.56 for quetiapine 600 mg/day. Responder rates (YMRS improvement ≥ 50 %) were 64 % for quetiapine 400 mg/day, 58 % for 600 mg/day and 37 % in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was –8.16 for quetiapine 400 mg/day and –9.29 for quetiapine 800 mg/day. Neither low dose (400 mg/day) nor high dose quetiapine regimen (800 mg/day) was superior compared to placebo with respect to the percentage of patients achieving response, defined as ≥ 30 % reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with quetiapine XR in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

Clinical safety

In the short-term paediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9 % vs. 5.3 % in the schizophrenia trial, 3.6 % vs. 1.1 % in the bipolar mania trial, and 1.1 % vs. 0 % in the bipolar depression trial. The rates of weight gain ≥ 7 % of baseline body weight in the active arm vs. placebo were 17 % vs. 2.5 % in the schizophrenia and bipolar mania trials, and 13.7 % vs. 6.8 % in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4 % vs. 1.3 % in the schizophrenia trial, 1.0 % vs. 0 % in the bipolar mania trial, and 1.1 % vs. 0 % in the bipolar depression trial. During an extended post-treatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

Long-term safety

A 26-week open-label extension to the acute trials (n = 380 patients), with quetiapine flexibly dosed at 400 to 800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see sections 4.4 and 4.8).

With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3 % of patients who were treated with quetiapine for at least 26 weeks met this criterion.

**5.2 Pharmacokinetic properties**

Absorption

Quetiapine is well absorbed and extensively metabolised following oral administration.

The bioavailability of quetiapine is not significantly affected when administered with food. Steady-state peak molar concentrations of the active metabolite norquetiapine are 35 % of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear across the approved dosing range.

Distribution

Quetiapine is approximately 83 % bound to plasma proteins.

Biotransformation

Quetiapine is extensively metabolised by the liver, with the parent compound accounting for less than 5 % of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine.

*In vitro* investigations showed that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

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

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450-mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in cytochrome P450 activity was found after administration of quetiapine.

Elimination

The elimination half life of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is < 5 % excreted in the urine.

Special populations

*Gender*

The pharmacokinetics of quetiapine does not differ between men and women.

*Elderly*

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

*Renal impairment*

The mean plasma clearance of quetiapine was reduced by approximately 25 % in patients with severe renal impairment (creatinine clearance less than 30 ml/min/1.73 m2), but the individual clearance values are within the range of normal patients.

*Hepatic impairment*

The mean plasma clearance of quetiapine was reduced by approximately 25% in patients with known hepatic impairment (stable alcoholcirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected and dose adjustments may be necessary in these patients (see section 4.2).

*Paediatric population*

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

**5.3 Preclinical safety data**

There was no evidence of genotoxicity in a series of *in vitro* and *in vivo* genotoxicity studies. The following deviations were observed in laboratory animals at a clinically relevant exposure level, but have not yet been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys, thyroid follicular cell hypertrophy, a lowering in plasma T3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs, lens opacity and cataracts have been oberved (for cataracts/lens opacities see section 5.1).

In an embryofoetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.

In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were observed. These effects are related to elevated prolactin levels and are not directly relevant for humans because of species differences in hormonal control of reproduction.

**6. PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

*Quetiapin "Lannacher" 25 mg film-coated tablets*

*Tablet core*

Calcium Hydrogen Phosphate, Anhydrous

Lactose Monohydrate

Cellulose, Microcrystalline

Sodium starch glycollate (Type A)

Povidone

Magnesium Stearate

*Tablet coating*

Polyvinyl alcohol

Lecithin

Titanium Dioxide (E171)

Macrogol 3350

Talc

Iron oxide yellow (E172)

Iron oxide red (E172)

*Quetiapin "Lannacher" 100 mg film-coated tablets*

*Tablet core*

Calcium Hydrogen Phosphate, Anhydrous

Lactose Monohydrate

Cellulose, Microcrystalline

Sodium starch glycollate (Type A)

Povidone

Magnesium Stearate

*Tablet coating*

Polyvinyl alcohol

Lecithin

Titanium Dioxide (E171)

Macrogol 3350

Talc

Iron oxide yellow (E172)

*Quetiapin "Lannacher" 200 mg film-coated tablets*

*Tablet core*

Calcium Hydrogen Phosphate, Anhydrous

Lactose Monohydrate

Cellulose, Microcrystalline

Sodium starch glycollate (Type A)

Povidone

Magnesium Stearate

*Tablet coating*

Polyvinyl alcohol

Lecithin

Titanium Dioxide (E171)

Macrogol 3350

Talc

*Quetiapin "Lannacher" 300 mg film-coated tablets*

*Tablet core*

Calcium Hydrogen Phosphate, Anhydrous

Lactose Monohydrate

Cellulose, Microcrystalline

Sodium starch glycollate (Type A)

Povidone

Magnesium Stearate

*Tablet coating*

Polyvinyl alcohol

Lecithin

Titanium Dioxide (E171)

Macrogol 3350

Talc

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

5 years.

**6.4 Special precautions for storage**

This medicinal product does not require any special storage conditions.

**6.5 Nature and contents of container**

PVC/PE/PVDC/Alu blister

Pack sizes

*Quetiapin "Lannacher" 25 mg film-coated tablets*

10, 30, 60 tablets (blister packs)

*Quetiapin "Lannacher" 100 mg film-coated tablets*

30, 60, 90 tablets (blister packs)

*Quetiapin "Lannacher" 200 mg film-coated tablets*

30, 60, 90 tablets (blister packs)

*Quetiapin "Lannacher" 300 mg film-coated tablets*

10, 20, 30, 60, 90 tablets (blister packs)

*Quetiapin "Lannacher" Starterpack*

1 blister with 6 tablets of Quetiapine 25 mg film-coated tablets

1 blister with 5 tablets of Quetiapine 100 mg film-coated tablets

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

Lannacher Heilmittel Ges.m.b.H

Schlossplatz 1

8502 Lannach

Østrig

**8. MARKETING AUTHORISATION NUMBER(S)**

25 mg: 40181

100 mg: 40182

200 mg: 40183

300 mg: 40184

Startpakke: 40185

**9. DATE OF FIRST AUTHORISATION**

 21 December 2007

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