Summary of activities in the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Important identified risks:	Extrapyramidal symptoms Somnolence Weight gain Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs) Hyperglycemia and diabetes mellitus Metabolic risk factors
Important potential risks:	Cerebrovascular adverse events in the elderly Cerebrovascular adverse events in the non-elderly patients Torsade de Pointes Ischemic heart disease Abuse and misuse Potential for off label use and misdosing Use in elderly patients
Important missing information:	Use in pregnant or breast feeding women Use in patients on concomitant cardiovascular medications Use in patients on concomitant valproic acid

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Extrapyramidal symptoms	(Proposed) content in SPC Section: **4.2 Posology and method of administration**	An educational program is in place by the

	Dosing schedules was different indications. **4.4 Special warnings and precautions for use** 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 and major depressive disorder. 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 Caution in children and adolescents as extrapyramidal symptoms may have different implications for children and adolescents. **4.6 Fertility, pregnancy and lactation** Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal symptoms. **4.8 Undesirable effects** Listed in this section; one of the most commonly reported ADRs. **5.1 Pharmacodynamic properties** Mentioning of studies. Other routine risk minimisation measures Prescription only medicine	originator to communicate and reinforce the core safety messages conveyed in the SmPC and PIL to increase the awareness that extrapyramidal symptoms can occur more commonly with quetiapine use in patients treated for major depressive episodes in bipolar disorder and major depressive disorder. All prescribing physicians who are expected to prescribe/use quetiapine will be distributed the educational material before the launch of Krka's product*. *if requested by the National Competent Authority
Somnolence	(Proposed) content in SPC Section: **4.2 Posology and method of administration** Dosing schedules was different indications. **4.4 Special warnings and precautions for use** In clinical trials for treatment of patients with bipolar depression and major depressive disorder, 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 onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered. **4.6 Fertility, pregnancy and lactation**	An educational program is in place by the originator to communicate and reinforce the core safety messages conveyed in the SmPC and PIL to increase the awareness that somnolence can occur more commonly with quetiapine use in patients treated for major depressive

	Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including somnolence. **4.7 Effects on ability to drive and use machines** Patients should be advised not to drive or operate machinery, until individual susceptibility to this is known. **4.8 Undesirable effects** Listed in this section; one of the most commonly reported ADRs. Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine. Other routine risk minimisation measures Prescription only medicine	episodes in bipolar disorder and major depressive disorder and that therefore quetiapine should be administered at bedtime. All prescribing physicians who are expected to prescribe/use quetiapine will be distributed the educational material before the launch of Krka's product*. *if requested by the National Competent Authority
Weight gain	(Proposed) content in SPC Section: **4.4 Special warnings and precautions for use** Warning in this section. **4.8 Undesirable effects** Listed in this section; one of the most commonly reported ADRs. **5.1 Pharmacodynamic properties** Mentioning of studies. Other routine risk minimisation measures Prescription only medicine	Educational material*. *if requested by the National Competent Authority
Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs)	(Proposed) content in SPC Section: **4.4 Special warnings and precautions for use** Warning in this section. **4.8 Undesirable effects** Listed in this section. Other routine risk minimisation measures Prescription only medicine	Educational material*. *if requested by the National Competent Authority
Hyperglycemia and diabetes mellitus	(Proposed) content in SPC Section: **4.4 Special warnings and precautions for use** Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has	Educational material*. *if requested by the National Competent Authority

	been reported rarely, including some fatal cases. **4.8 Undesirable effects** Listed in this section. Other routine risk minimisation measures Prescription only medicine	
Metabolic risk factors	Proposed) content in SPC Section: **4.4 Special warnings and precautions for use** Changes in weight, blood glucose and lipids are seen in clinical studies. Patients may experience worsening of their metabolic risk profile, which should be managed as clinically appropriate. **4.8 Undesirable effects** Listed in this section. Other routine risk minimisation measures Prescription only medicine	Educational material*. *if requested by the National Competent Authority
Cerebrovascular adverse events in the elderly patients	(Proposed) content in SPC Section: **4.4 Special warnings and precautions for use** Quetiapine is not approved for the treatment of dementia-related psychosis. An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. Quetiapine should be used with caution in patients with risk factors for stroke. Other routine risk minimisation measures Prescription only medicine	None proposed
Cerebrovascular adverse events in the non-elderly patients	The relatedness of Cerebrovascular AEs in the non-elderly patients to quetiapine administration has not been confirmed yet.	None proposed
Torsade de Pointes	(Proposed) content in SPC Section: **4.8 Undesirable effects** Listed in this section. 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. Other routine risk minimisation measures Prescription only medicine	None proposed
Ischemic heart disease	The relatedness of ischemic heart disease to quetiapine administration has not been	None proposed

	confirmed yet.	
Abuse and misuse	The relatedness of abuse and misuse to quetiapine administration has not been confirmed yet.	None proposed
Potential for off label use and misdosing	Clear guidance provided in Sections **4.1 Therapeutic indications** and **4.2 Posology and method of administration** Other routine risk minimisation measures Prescription only medicine	None proposed
Use in elderly patients	(Proposed) content in SPC Section: **4.2 Posology and method of administration** Quetiapine should be used with caution in elderly patients, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients. **5.1 Pharmacodynamic properties** Data on studies in the elderly. **5.2 Pharmacokinetic properties** The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years. Other routine risk minimisation measures Prescription only medicine	None proposed
Use in pregnant or breast feeding women	(Proposed) content in SPC Section: **4.6 Fertility, pregnancy and lactation** The safety and efficacy of quetiapine during human pregnancy have not yet been established. Quetiapine should only be used during pregnancy if the benefits justify the potential risks. Neonatal withdrawal symptoms were observed after exposures during the third trimester of pregnancy. There have been published reports of quetiapine excretion into human breast milk. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine. **4.8 Undesirable effects** Drug withdrawal syndrome neonatal is listed in this section. Other routine risk minimisation measures Prescription only medicine	None proposed

Use in patients on concomitant cardiovascular medications	(Proposed) content in SPC Section: **4.5 Interaction with other medicinal products and other forms of interaction** Formal interaction studies with commonly used cardiovascular medicinal products have not been performed. Other routine risk minimisation measures Prescription only medicine	None proposed
Use in patients on concomitant valproic acid	(Proposed) content in SPC Section: **4.5 Interaction with other medicinal products and other forms of interaction** The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups. Other routine risk minimisation measures Prescription only medicine	None proposed

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Incidence and prevalence of target indication	schizophrenia Schizophrenia is a mental disorder characterized by a breakdown of thought processes and by impaired emotional responses. Common symptoms are delusions including paranoia and auditory hallucinations, disorganized thinking reflected in speech, and a lack of emotional intelligence. It is accompanied by significant social or vocational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of about 0.3–0.7%. Diagnosis is based on observed behavior and the patient's reported experiences. bipolar disorder; moderate to severe manic episodes Bipolar disorder, also known as bipolar affective disorder, manic-depressive disorder, or manic depression, is a mental illness classified by psychiatry as a mood disorder. Individuals with bipolar disorder experience episodes of an elevated or agitated mood known as mania alternating with episodes of depression. 2.4 percent of the world's population may have some

form of the disease.
Mania can occur with different levels of severity. At milder levels of mania, known as hypomania, individuals appear energetic, excitable, and may be highly productive. As mania becomes more severe, individuals begin to behave erratically and impulsively, often making poor decisions due to unrealistic ideas about the future, and may have great difficulty with sleep. At the most severe level, individuals can experience very distorted beliefs about the world known as psychosis.

bipolar disorder; major depressive episodes

2.4 percent of the world's population may have some form of bipolar disorder.
Signs and symptoms of the depressive phase of bipolar disorder include persistent feelings of sadness, anxiety, guilt, anger, isolation, or hopelessness; disturbances in sleep and appetite; fatigue and loss of interest in usually enjoyable activities; problems concentrating; loneliness, self-loathing, apathy or indifference; depersonalization; loss of interest in sexual activity; shyness or social anxiety; irritability, chronic pain (with or without a known cause); lack of motivation; and morbid suicidal thoughts. In severe cases, the individual may become psychotic, a condition also known as severe bipolar depression with psychotic features. These symptoms include delusions or, less commonly, hallucinations, usually unpleasant. A major depressive episode persists for at least two weeks, and may continue for over six months if left untreated.

Prevention of recurrence in patients with bipolar disorder, in patients whose manic, mixed or depressive episode has responded to quetiapine treatment

A naturalistic study from first admission for mania or mixed episode (representing the hospitalized and therefore most severe cases) found that 50% achieved syndromal recovery (no longer meeting criteria for the diagnosis) within six weeks and 98% within two years. Within two years, 72% achieved symptomatic recovery (no symptoms at all) and 43% achieved functional recovery (regaining of prior occupational and residential status). However, 40% went on to experience a new episode of mania or depression within 2 years of syndromal recovery, and 19% switched phases without recovery.

Add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy

Major depressive disorder (MDD) is a mental disorder characterized by a pervasive and persistent low mood which is accompanied by low self-esteem and by a loss of interest or

pleasure in normally enjoyable activities. Major depressive disorder is a disabling condition that adversely affects a person's family, work or school life, sleeping and eating habits, and general health. It is believed to currently affect approximately 298 million people as of 2010 (4.3% of the global population). Lifetime prevalence varies widely, from 3% in Japan to 17% in the US. In the United States, around 3.4% of people with major depression commit suicide, and up to 60% of people who commit suicide had depression or another mood disorder.

VI.2.2 Summary of treatment benefits

Clinical studies show that patients can be switched to and from quetiapine without much difficulty. Quetiapine's efficacy is clearly superior to that of placebo, is similar to that of haloperidol or chlorpromazine, and appears to have similar efficacy to risperidone and olanzapine. It has a benign side-effect profile, particularly regarding to extrapyramidal symptoms and therefore good compliance is expected. Generally quetiapine is considered a safe drug.

Although quetiapine was introduced as an atypical antipsychotic drug with clinical efficacy in schizophrenic patients, there is also new evidence from studies regarding its efficacy in treating mood disorders (bipolar disorder). To date, quetiapine has demonstrated efficacy in both acute mania and bipolar depression, with a safety and tolerability profile superior to other medications in its class.

Quetiapine has also demonstrated efficacy in treating bipolar disorder in paediatric and geriatric populations. Quetiapine has been examined in children and adolescents in randomized clinical trials, open-label studies and several chart review studies. Most studies indicate that quetiapine is effective and well tolerated in paediatric population.

Also, in long-term studies (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder.

Also, two short-term (6 week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. Quetiapine prolonged release 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms.

VI.2.3 Unknowns relating to treatment benefits

Not applicable. This is a generic application.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
<Safety concern in lay language (medical term)>	<Brief summary in lay language>	<Whether risk can be minimised or mitigated, and how>
Abnoramal muscle movement/symptoms similar to Parkinson's disease	In placebo controlled clinical trials of adult patients quetiapine was	Extrapyramidal symptoms include difficulty starting muscle movements, shaking,

Risk	What is known	Preventability
(Extrapyramidal symptoms)	associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder.	feeling restless or muscle stiffness without pain and other symptoms similar to Parkinson's disease.
Feeling sleepy (Somnolence)	Quetiapine treatment has been associated with feeling sleepy (somnolence) and related symptoms, such as sedation. In clinical trials for treatment of patients with bipolar depression, the onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. In patients experiencing somnolence of severe intensity discontinuation of quetiapine may need to be considered.	Feeling sleepy (this may go away with time) (may lead to falls); however, in more severe cases discontinuation of quetiapine may need to be considered.
Weight gain	Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate.	Weight gain has been seen in patients taking quetiapine. The patient and his/her doctor should check the patient's weight regularly.
Changes/increases in the content of certain fats in blood (Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs))	Changes/increases in the content of certain fats in blood (Increases in triglycerides, LDL cholesterol and total cholesterol, and decreases in HDL cholesterol) have been observed in clinical trials with quetiapine. Lipid changes should be managed as clinically appropriate.	The doctor may weigh the patient and may be checking for certain fats in the blood while the patient is receiving quetiapine therapy.
Increases in blood sugar (Hyperglycemia) and diabetes mellitus	Increases in blood sugar (Hyperglycaemia) and/or development or exacerbation of diabetes occasionally associated with a very severe consequences, called ketoacidosis or coma, has been reported rarely, including some fatal cases. In some cases, a prior increase in body weight has	Before taking the medicine, the doctor needs to be told if the patient has diabetes or a risk of getting diabetes. If this is the case, the doctor may check the patient's blood sugar levels while the patient is taking quetiapine.

Risk	What is known	Preventability
	been reported which may be a predisposing factor.	
Risk factors that make you prone to gain weight, develop diabetes and increase the content of different fats in blood (Metabolic risk factors)	Given the observed changes in weight, blood glucose and lipids seen in clinical studies, patients (including those with normal baseline values) may experience worsening of their metabolic risk profile, which should be managed as clinically appropriate.	The doctor may weigh the patient and may be checking his/her blood sugar and certain fats in his/her blood while the patient is taking quetiapine.

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Stroke in elderly patients (Cerebrovascular adverse events in the elderly)	An approximately 3-fold increased risk of cerebrovascular adverse events has been seen 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.
Stroke in non-elderly patients (Cerebrovascular adverse events in the non-elderly patients)	As some cases have been identified, this adverse event is considered a potential risk.
Life-threatening arrhythmia (Torsade de Pointes)	Neuroleptics have been associated with the development of various life-threatening arrhythmias (such as QT-prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes), which can lead to sudden death. This is considered a class effect.
Heart disease caused by a decrease in blood perfusion (Ischemic heart disease)	As some cases have been identified, this adverse event is considered a potential risk.
Abuse and misuse	As some cases have been identified, this adverse event is considered a potential risk.
Potential for using the drug different than what it is intended for (Potential for off label use and misdosing)	There is clear guidance provided on the usage of quetiapine. However, there have been cases when quetiapine has been used for indications and at dosages it is not approved for.
Use in elderly patients	The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients. Therefore, quetiapine should be used with caution in elderly patients, especially during the initial dosing period. The rate of dose titration may need to be slower, and the daily therapeutic dose lower, than that used in younger patients.

Important missing information

Risk	What is known
Use in pregnant or breast feeding women	Pregnancy: The safety and efficacy of quetiapine during human pregnancy have not yet been established. Up to now there are no indications for harmfulness in animal tests, possible effects on the foetal eye have not been examined, though. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks. Following pregnancies in which quetiapine was used, neonatal withdrawal symptoms were observed. 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: There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine. If the patient is pregnant or breast-feeding, thinks she may be pregnant or is planning to have a baby, she needs to ask her doctor or pharmacist for advice before taking this medicine. The patient should not take quetiapine during pregnancy unless this has been discussed with her doctor. Quetiapine should not be taken if the patient is breast-feeding. The following symptoms may occur in newborn babies, of mothers that have used quetiapine in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If the patient's baby develops any of these symptoms the patient may need to contact her doctor.
Use in patients on concomitant cardiovascular medications	Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.
Use in patients on concomitant valproic acid	The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leukopenia and neutropenia in the combination group versus the monotherapy groups.

VI.2.5 Summary of additional risk minimisation measures by safety concern
The following additional risk minimisation measures are considered necessary.

Risk: Weight gain
Risk minimization measure: Healthcare Professional education
Objective and rationale: To inform all prescribing physicians, prior to launch of quetiapine by Krka, that weight gain can occur with quetiapine use and that patients need to be counseled, monitored and treated accordingly.
Main additional risk minimization measures: HCP educational materials to be provided to all prescribing physicians prior to launch of Quetiapine by Krka*. *if requested by the National Competent Authority.

Risk: Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs)
Risk minimization measure: Healthcare Professional education
Objective and rationale: To inform all prescribing physicians, prior to launch of quetiapine by Krka, that lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs) can occur with quetiapine use and that patients need to be counseled, monitored and treated accordingly.
Main additional risk minimization measures: HCP educational materials to be provided to all prescribing physicians prior to launch of Quetiapine by Krka*. *if requested by the National Competent Authority

Risk: Hyperglycemia and diabetes mellitus
Risk minimization measure: Healthcare Professional education
Objective and rationale: To inform all prescribing physicians, prior to launch of quetiapine by Krka, that hyperglycemia and diabetes mellitus can occur with quetiapine use and that patients need to be counseled, monitored and treated accordingly.
Main additional risk minimization measures: HCP educational materials to be provided to all prescribing physicians prior to launch of Quetiapine by Krka*. *if requested by the National Competent Authority.

Risk: Metabolic risk factors
Risk minimization measure: Healthcare Professional education
Objective and rationale: To inform all prescribing physicians, prior to launch of quetiapine by Krka, that metabolic risk factorscan occur with quetiapine use and that patients need to be counseled, monitored and treated accordingly.

Main additional risk minimization measures: HCP educational materials to be provided to all prescribing physicians prior to launch of Quetiapine by Krka*. *if requested by the National Competent Authority.

Risk: Extrapyramidal symptoms
Risk minimization measure: Healthcare Professional education
Objective and rationale: To inform all prescribing physicians, prior to launch of quetiapine by Krka, that extrapyramidal symptoms can occur with quetiapine use in patients treated for major depressive episodes in bipolar disorder and major depressive disorder and that patients need to be counseled, monitored and treated accordingly.
Main additional risk minimization measures: An educational program is in place by the originator to communicate and reinforce the core safety messages conveyed in the SmPC and PIL. HCP educational materials to be provided to all prescribing physicians prior to launch of Quetiapine by Krka*. *if requested by the National Competent Authority.

Risk: Somnolence
Risk minimization measure: Healthcare Professional education
Objective and rationale: To inform all prescribing physicians, prior to launch of quetiapine by Krka, that somnolence can occur with quetiapine use in patients treated for major depressive episodes in bipolar disorder and major depressive disorder and that patients need to be counseled, monitored and treated accordingly.
Main additional risk minimization measures: An educational program is in place by the originator to communicate and reinforce the core safety messages conveyed in the SmPC and PIL. HCP educational materials to be provided to all prescribing physicians prior to launch of Quetiapine by Krka*. *if requested by the National Competent Authority.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable. No postauthorisation studies are planned.