Biquetan 50, 150, 200, 300 & 400 mg prolonged release tablets

6.12.2016, Version V4.0

PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Schizophrenia is a serious brain illness. Many people with schizophrenia are disabled by their symptoms.

People with schizophrenia may hear voices other people don't hear. They may think other people are trying to hurt them. Sometimes they don't make any sense when they talk. The disorder makes it hard for them to keep a job or take care of themselves.
Anyone can develop schizophrenia. It affects men and women equally in all ethnic groups. Teens can also develop schizophrenia. In rare cases, children have the illness too.
Several factors may contribute to schizophrenia, including:

- Genes, because the illness runs in families
- The environment, such as viruses and nutrition problems before birth
- Different brain structure and brain chemistry.

Schizophrenia symptoms range from mild to severe. Schizophrenia's symptoms includes hallucinations, delusions, through disorders, movement disorders, difficulty showing emotions or functioning normally, trouble using information to make decisions, problems using information immediately after learning it, trouble paying attention.

Bipolar disorder is a serious brain illness. It is also called manic-depressive illness. People with bipolar disorder go through unusual mood changes. Sometimes they feel very happy and "up," and are much more active than usual. This is called mania. And sometimes people with bipolar disorder feel very sad and "down," and are much less active. This is called depression. Bipolar disorder can also cause changes in energy and behavior. Bipolar disorder is not the same as the normal ups and downs everyone goes through. Bipolar symptoms are more powerful than that. They can damage relationships and make it hard to go to school or keep a job. They can also be dangerous. Some people with bipolar disorder try to hurt themselves or attempt suicide. People with bipolar disorder can get treatment. With help, they can get better and lead successful lives.
Anyone can develop bipolar disorder. The illness usually lasts a lifetime.

Major depressive disorder (MDD) is a mental disorder characterized by a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. It adversely affects a person's family, work or school life, sleeping and eating habits, and general health. 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. Depressive disorders are more common to observe in urban than in rural population. MDD will be the second leading cause of burden of disease worldwide by 2030. The annual incidence rate (number of new cases per population at risk) of MDD is about 1 to 8%. People are most likely to suffer their first depressive episode between the ages of 30 and 40, and there is a second, smaller peak of occurrence between ages 50 and 60.

VI.2.2 Summary of treatment benefits

Quetiapine is an atypical antipsychotic medication approved for the treatment of schizophrenia. At this time, it is only approved for use in adults.

In clinical studies people taking the drug for schizophrenia experienced improvement in their schizophrenia symptoms (including hallucinations and suspiciousness) when compared to those not taking the drug. Quetiapine appears to have minimal short-term effects on bodyweight and a favourable long-term bodyweight profile. In addition, quetiapine has shown efficacy against both positive and negative symptoms of schizophrenia, and has benefits in improving mental deficits, affective symptoms and aggression/hostility.
Quetiapine is also approved for the treatment of bipolar disorder in adults. Bipolar disorder symptoms can result in damaged relationships, poor job or school performance, and even suicide. But bipolar disorder can be treated, and people with this illness can lead full and productive lives.
Quetiapine common adverse events include dry mouth, sedation, somnolence, dizziness, and constipation. In clinical studies the incidence of treatment-emergent mania or hypomania was lower with quetiapine treatment when compared to those patients not taking the drug.
Approximately half of the patients with major depressive disorder (MDD) respond insufficiently to current antidepressants, resulting in increased risk of deterioration and remaining symptoms. Quetiapine is also used as adjunct treatment to antidepressant monotherapy.
Efficacy and tolerability of quetiapine use adjunct to index antidepressant therapy in patients with major depression disorder were assessed in different studies. Quetiapine significantly improved depressive symptoms versus patients not taking the drug. Significant improvement in quality of life versus patients not taking the drug was confined to elderly patients with major depressive disorder. Tolerability was consistent with the known pharmacological profile of quetiapine: the most common adverse events were dry mouth, somnolence, sedation, dizziness and fatigue.

VI.2.3 Unknowns relating to treatment benefits

In a number of published studies quetiapine has shown benefits for non-approved indications.

Borderline personality disorder
Individuals with borderline personality disorder (BPD) suffer from symptoms that include a combination of impulsivity, aggression, self-injury, behavioral dysregulation, mood instability, aggressiveness, cognitive–perceptual difficulties, anxiety and unstable relationships. Overall, the prescription of quetiapine in personality disorders appears to lead to significant improvements in depression and anxiety.

Post-traumatic stress disorder (PTSD)
Quetiapine generally appears to be very effective in trauma-related conditions by improving autonomic stability, and decreasing the stress and anxiety response that arises due to specific fears or triggers. Studies suggest that quetiapine provides an important pharmacological adjunct in the treatment of PTSD either as monotherapy or as augmentation to existing medications.

Obsessive–compulsive disorder (OCD)
Quetiapine has recently been found to be affective in improving symptoms in OCD patients that do not respond to pharmacological or psychological interventions. Tolerability is also found to be very good with adverse effects being generally temporary.

Substance abuse
Success has been documented in the application of quetiapine in substance abuse. This has generally been in the presence of significant comorbid psychiatric conditions so it is not clear whether the therapeutic effects of quetiapine act via normalization of the primary or secondary psychiatric symptom or both.

Depression

An antipsychotic is generally only recommended in depressed patients showing psychotic features. However, the therapeutic affects of quetiapine on depressive symptoms has now been documented across a wide range of psychiatric conditions, including major depressive disorder without psychotic features.

Anxiety
Quetiapine is a potential alternative for patients suffering from treatment-resistant anxiety disorder. Its efficacy and tolerability has already been illustrated in more specific anxiety disorders such as OCD and PTSD.

Other off-label indications included:

1. Quetiapine use for benefit in patients with severe functional symptoms of irritable bowel syndrome who are not receiving adequate relief from their symptoms from their present regimen of a selective norepinephrine reuptake inhibitor (SNRI) or a tricyclic antidepressant agent (TCA).
2. Quetiapine use in patients with delirium

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Inability to initiate movement, inability to remain motionless. (Extrapyramidal symptoms)	The use of quetiapine has been associated with the development of inability to remain motionless 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. Abnormal muscle movements including difficulty of starting muscle movements, shaking, feeling restless or muscle stiffness without pain may also occur.	This adverse event may affect up to 1 in 100 people. Physician should be advised if such symptoms occur. In patients who develop these symptoms, increasing of the dose should be avoided.
Sleepiness (Somnolence)	Somnolence is a state of nearsleep, a strong desire for sleep, or sleeping for unusually long periods. In clinical trials, the onset of somnolence occurs usually within the first 3 days of treatment and was predominantly of mild to moderate intensity.	This adverse event may affect up to 1 in 10 people. Patient should be very careful in his activities (e.g avoid driving) and physician should be advised if such symptoms occur.
Weight gain	Treatment with quetiapine has been associated with moderate weight gain. Most of the weight gain (greater than 60%) appears to occur within the first 12 weeks of therapy with modest changes occurring after 6 months. In one study, the mean weight gain after 1 and 2 years of treatment with quetiapine was 3.19 kg and 5.16 kg, respectively. The weight gain reported with quetiapine does not appear to be dose-related.	This adverse event may affect more than 1 in 10 people. It should be monitored and managed as clinically appropriate by the physician.
Changes in the amount of certain fats (triglycerides and cholesterol)	Cholesterol is a waxy substance that's found in the fats (lipids) in the blood. While body needs	This adverse event may affect more than 1 in 10 people. This side effect is only seen when a

(Lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs))	cholesterol to continue building healthy cells, having high cholesterol can increase risk of heart disease (e.g by developing fatty deposits in the blood vessels). Triglycerides are the major form of fat stored by the body. Elevated triglyceride levels are considered to be a risk factor for atherosclerosis (hardening of the arteries) because many of the triglyceride-containing lipoproteins that transport fat in the bloodstream also transport cholesterol, a known contributor to atherosclerosis.	blood test is taken. Available data show that cholesterol and triglycerides increase on at least one occasion during treatment with quetiapine. It should therefore be monitored as clinically appropriate by the physician.
Increased levels of sugar in the blood (Hyperglycemia and diabetes mellitus)	Hyperglycaemia and/ or development or exacerbation of diabetes occasionally associated with ketoacidosis (accumulation of ketone bodies in the blood) or coma has been reported rarely, including some fatal cases. 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 utilized antipsychotic guidelines.	This adverse event may affect more than 1 in 10 people. 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.
Weight, blood glucose and lipids changes (Metabolic risk factors)	Metabolic syndrome is a disorder of energy utilization and storage, diagnosed by a co-occurrence of three out of five of the following medical conditions: abdominal (central) obesity, elevated blood pressure, elevated fasting plasma glucose, high serum triglycerides, and low high-density cholesterol (HDL) levels. Metabolic syndrome increases the risk of developing cardiovascular disease, particularly heart failure, and diabetes.	Given the observed changes in weight, blood glucose (see hyperglycemia) and lipids seen in clinical studies, patient's metabolic risk profile may experience worsening. Thus, these adverse events should be managed by the physician as clinically appropriate.

Change in electrical activity of the heart seen on ECG (QT prolongation)	The Q-T interval is the section on the electrocardiogram (ECG) - that represents the time it takes for the electrical system to fire an impulse through the ventricles and then recharge. It is translated to the time it takes for the heart muscle to contract and then recover. In post marketing data, QT prolongation was reported with quetiapine at the therapeutic doses.	As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia. Thus, patient should inform physician if has any cardiovascular disease or family history of QT prolongation and if other medicines are taken.

Important potential risks

Risk	**What is known** **(Including reason why it is considered a potential risk)**
Cerebrovascular AEs the elderly	In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Quetiapine is not approved for the treatment of patients with dementia-related psychosis.
Cerebrovascular AEs in the non-elderly patients	Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Quetiapine may induce orthostatic hypotension especially during the initial dose-titration period and therefore dose reduction or more gradual titration should be considered if this occurs. A slower titration regimen could be considered in patients with underlying cardiovascular disease.
Torsades de Pointes	Prolongation of the QT interval is associated with a greater risk of arrhythmia and sudden cardiac death. Studies exploring the higher rates of sudden death in patients with schizophrenia suggest antipsychotic-associated QT prolongation and resulting torsade de pointes (TdP) as possible etiologies.
Ischemic heart disease	Persons with schizophrenia die earlier than the general population, in large part due to cardiovascular disease. The study objective was to examine effects of different antipsychotic treatments on estimates of 10 year coronary heart disease (CHD) risk calculated by the Framingham Heart Study formula. Quetiapine was associated with a 0.3% increase of death. Thus, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the

	elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.
Abuse and misuse	Quetiapine has been cited in several recent reports of being abused, especially in prison settings under the name “baby heroin” and “quell.” Methods of quetiapine misuse include ingesting pills, inhaling crushed tablets, and injecting a solution of dissolved tablets. In case studies, patients report abusing quetiapine for its sedative, anxiolytic, and calming effects. Clinicians must differentiate inmates who have legitimate psychiatric symptoms that require antipsychotic treatment from those who are malingering to obtain the drug.
Suicide and suicidality	Depression 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 observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders. Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should 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 present. 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 adults patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (substance having no pharmacological effect). In clinical studies of patients with major depression disorder the incidence (the number of times an event occurs) of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo.

Potential for off-label use and misdosing	Atypicals antipsychotics such as quetiapine have been studied as off-label treatment for the following conditions: attention-deficit hyperactivity disorder (ADHD), anxiety, dementia in elderly patients, major depressive disorder, eating disorders, insomnia, obsessive-compulsive disorder (OCD), personality disorder, post-traumatic stress disorder (PTSD), substance use disorders, and Tourette's syndrome.

Missing information

Risk	What is known
Use in pregnant or breast feeding women	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. 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.
Use in patients on concomitant cardiovascular medications	Formal interaction studies with commonly used cardiovascular medicinal products 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.
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 leucopenia and neutropenia in the combination group versus the monotherapy groups. However, there are studies suggesting that further search are required to investigate the potential of therapeutic drug monitoring as a clinical tool in improving pharmacotherapy and preventing toxicity

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). An educational program has been set up for healthcare professionals to help them minimise the occurrence of the following risks:

- Extrapyramidal symptoms
- Somnolence
- Metabolism and nutritional disorders (weight gain)
- Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs)

- Hyperglycamia and diabetes mellitus
- Metabolic risk factors
- Potential for off-label use and misdosing

VI.2.6 Planned post authorisation development plan

No post-authorisation studies have been imposed or are planned.

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety concerns	Comment
1.0	06.06.2013	NA	Initial version
2.0	15.05.2014	Important identified risks •Extrapyramidal symptoms •Tardive dyskinesia •Somnolence •Syncope and orthostatic hypotension •Seizure •Dysarthria •Neutropenia •Agranulocytosis •Weight gain •Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs) •Hyperglycemia and diabetes mellitus •Metabolic risk factors •Hyponatraemia and SIADH •Hypothyroidism •Hyperprolactinemia •Anaphylactic reaction •Jaundice, hepatitis, increased transaminases and GGT •Stevens-Johnson Syndrome •Neuroleptic malignant syndrome •Withdrawal (discontinuation) symptoms and Neonatal withdrawal •Rhabdomyolysis •Dysphagia •Pancreatitis •Intestinal obstruction •QT prolongation •Venous thromboembolism •Increased blood pressure in the paediatric population Important potential risks •Cerebrovascular adverse effects in elderly patients	Implementation of Assessor (day 70 +100) comments Implementation of updated EU template of generic RMP (EMA/465932/2013 Rev.1 of 25 July 2013)

		•Cerebrovascular adverse effects in nonelderly patients •Serotonin syndrome •Torsades de Pointes •Sudden death •Myocarditis •Ischemic heart disease •Cataract •Increased mortality in elderly demented patients •Aggression/agitation •Abuse and misuse •Suicide and suicidality •Accidental injury •Aspiration pneumonia •Potential for off-label use and misdosing •Use in patients with hepatic impairment •Use in elderly patients •Treatment emergent mania in bipolar disorder Missing information •Use in patients with renal impairment •Use in patients with hepatic impairment •Use in pregnant or lactating women •Use in patients of different racial or ethnic origin •Use in patients on concomitant cardiovascular medications •Use in patients on concomitant valproic acid •Use in patients with longer-term exposure	
3.0	17.09.2014	Important identified risks •Extrapyramidal symptoms •Tardive dyskinesia •Somnolence •Syncope and orthostatic hypotension •Seizure •Dysarthria •Neutropenia •Agranulocytosis •Weight gain •Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs) •Hyperglycemia and diabetes mellitus	Day 120 RMS Assessment

		•Metabolic risk factors •Hyponatraemia and SIADH •Hypothyroidism •Hyperprolactinemia •Anaphylactic reaction •Jaundice, hepatitis, increased transaminases and GGT •Stevens-Johnson Syndrome •Neuroleptic malignant syndrome •Withdrawal (discontinuation) symptoms and Neonatal withdrawal •Rhabdomyolysis •Dysphagia •Pancreatitis •Intestinal obstruction •QT prolongation •Venous thromboembolism •Increased blood pressure in the paediatric population Important potential risks •Cerebrovascular adverse effects in elderly patients •Cerebrovascular adverse effects in nonelderly patients •Serotonin syndrome •Torsades de Pointes •Sudden death •Myocarditis •Ischemic heart disease •Cataract •Increased mortality in elderly demented patients •Aggression/agitation •Abuse and misuse •Suicide and suicidality •Accidental injury •Aspiration pneumonia •Potential for off-label use and misdosing •Use in patients with hepatic impairment •Use in elderly patients •Treatment emergent mania in bipolar disorder Missing information •Use in patients with renal impairment •Use in patients with hepatic impairment •Use in pregnant or lactating women	

		•Use in patients of different racial or ethnic origin •Use in patients on concomitant cardiovascular medications •Use in patients on concomitant valproic acid •Use in patients with longer-term exposure	
4.0	06.12.2016	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 •QT prolongation Important potential risks •Cerebrovascular AEs in the elderly •Cerebrovascular AEs in the non-elderly patients •Torsades de pointes •Ischemic heart disease •Abuse and misuse •Suicide and suicidality •Potential for off label use and misdosing Missing information •Use in pregnant or breast feeding women •Use in patients on concomitant cardiovascular medications •Use in patients on concomitant valproic acid	Commitment from Repeat Use Procedure DK/H/2333/001-005/E/001