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**
Safety concern in lay language ***(medical term)***	**Brief summary in lay language**	**Whether risk can be minimised or mitigated, and how**
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	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

	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	
Involuntary, repetitive body movements *(Tardive dyskinesia)*	Tardive dyskinesia is a disorder resulting in involuntary, repetitive body movements most frequently occurs as the result of long-term or high-dose use of antipsychotic drugs such as quetiapine	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.
Sleepiness *(Somnolence)*	Somnolence is a state of near-sleep, 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.
Fainting and low blood pressure *(Syncope and orthostatic hypotension)*	*Syncope* is the medical term for fainting or passing out, defined as a transient loss of consciousness and postural tone, characterized by rapid onset, short duration, and spontaneous recovery, due to global cerebral hypoperfusion (low blood flow to the brain) that most often results from hypotension (low blood pressure). *Orthostatic hypotension*, also known as postural hypotension is a form of hypotension in which a person's blood pressure suddenly falls when standing up or stretching.	Quetiapine treatment has been associated with orthostatic hypotension and related dizziness which, like somnolence has 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.
Fits *(Seizure)*	A seizure is a sudden disruption of the brain's normal electrical activity accompanied	This adverse event may affect up to 1 in 100 people. Caution is recommended when treating

	by altered consciousness and/or other neurological and behavioral manifestations	patients with a history of seizures
Disturbance in speech and language *(Dysarthria)*	Dysarthria is the imperfect articulation of speech due to disturbances of muscular control resulting from central or peripheral nervous system damage.	This adverse event may affect up to 1 in 10 people. Physician should be advised if such symptoms occur.
Low level of white blood in the blood cells *(Neutropenia)*	Neutropenia is an abnormally low level of neutrophils in the blood. Neutrophils are white blood cells produced in the bone marrow that ingest bacteria. Neutropenia is a serious disorder because it makes the body vulnerable to bacterial and fungal infections.	Decreases in the number of certain types of blood cells may occur with quetiapine treatment. This side effect is only seen when a blood test is taken. 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. Physician should ask to have blood tests from time to time.
Combination of fever, flu-like symptoms, sore throat, or any other infection with very low white blood cell count *(Agranulocytosis)*	Neutropenia is sometimes called agranulocytosis because neutrophils make up about 60% of white blood cells and have granules inside their cell walls.	
Putting on weight *(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	*Cholesterol* is a waxy	This adverse event may affect

certain fats (triglycerides and cholesterol) *(Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs))*	substance that's found in the fats (lipids) in the blood. While body needs 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.	more than 1 in 10 people. This side effect is only seen when a 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 utilised 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	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

	increases the risk of developing cardiovascular disease, particularly heart failure, and diabetes.	
Low sodium ion concentration in the plasma and inappropriate secretion of a hormone that controls urine volume *(Hyponatraemia and SIADH)*	Hyponatremia is an electrolyte disturbance in which the sodium ion concentration in the plasma is lower than normal. The syndrome of inappropriate antidiuretic hormone secretion is characterized by excessive release of antidiuretic hormone from the posterior pituitary gland or another source.	This adverse event may affect up to 1 in 100 people. This side effect is only seen when a blood test is taken. Physician may ask to have blood tests from time to time
Severe allergic reaction which may cause difficulty in breathing or shock *(Anaphylactic reaction)*	Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death. It typically causes a number of symptoms including an itchy rash, throat swelling, and low blood pressure. Common causes include insect bites/stings, foods, and medications.	This adverse event may affect up to 1 in 10,000 people. However, patient should immediately advise physician as anaphylactic reaction may be life-threatening condition.
Yellowish of the skin and eyes, inflammation of the liver, increased hepatic enzymes *(Jaundice, hepatitis, increased transaminases and GGT)*	Asymptomatic elevations in serum transaminase (ALT, AST) or gamma-GT-levels have been observed in some patients administered quetiapine. These elevations are usually reversible on continued quetiapine treatment.	Asymptomatic elevation in hepatic enzymes may affect up to 1 in 10 people. This side effect may be monitor by blood test. Jaundice and hepatitis occur rarely (may affect up to 1 in 1,000 people), however in the apparition of any sign, physician should be advised.
Severe rash, blisters, or red patches on the skin *(Stevens-Johnson Syndrome)*	Stevens-Johnson syndrome is a rare, serious disorder of the skin and mucous membranes. It's usually a reaction to a medication or an infection. Often, Stevens-Johnson syndrome begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters. Then the top layer of the affected skin	Stevens-Johnson syndrome is a medical emergency that usually requires hospitalization. Therefore, patient should immediately after apparition of such symptoms, to advise physician.

	dies and sheds.	
A combination of fever, severe muscle stiffness, sweating or a lowered level of consciousness *(Neuroleptic malignant Syndrome)*	Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine. A combination of high temperature (fever), sweating, stiff muscles, feeling very drowsy or faint, lowered level of consciousness are symptoms of this syndrome.	Neuroleptic malignant syndrome (NMS) is a life-threatening neurological disorder. Therefore, if such events occur, quetiapine should be discontinued and appropriate medical treatment given.
Symptoms which occur when patient stop taking medication *(Withdrawal (discontinuation) symptoms and Neonatal withdrawal)*	Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. In addition, in neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy have been reported agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder.	Gradual withdrawal over a period of at least one to two weeks is advisable.
Breakdown of muscle fibers and pain in muscles *(Rhabdomyolysis)*	Rhabdomyolysis is a condition in which damaged skeletal muscle breaks down rapidly. Breakdown products of damaged muscle cells are released into the bloodstream; some of these, such as the protein myoglobin, are harmful to the kidneys and may lead to kidney failure.	This adverse event may affect up to 1 in 10,000 people. However, patient should immediately advise physician if pain of muscles occur, because rhabdomyolsis may lead to kidney failure.
Difficulty swallowing *(Dysphagia)*	Difficulty swallowing (dysphagia) means it takes more time and effort to move food or liquid from the mouth to the stomach. It may also be associated with pain.	Difficulty swallowing has been reported with quetiapine (especially in cases of bipolar depression). Thus, physician should immediately be advised if difficulty swallowing occurs
Inflammation of the pancreas *(Pancreatitis)*	Pancreatitis has been reported with quetiapine treatment. Pancreatitis is an inflammation in the pancreas. The pancreas	Among post marketing reports of quediapine treatment where pancreatitis has been occurred many patients had factors

	is a long, flat gland that sits tucked behind the stomach in the upper abdomen. The pancreas produces enzymes that assist digestion and hormones that help regulate the way your body processes sugar (glucose). Pancreatitis can occur as acute pancreatitis — meaning it appears suddenly and lasts for days. Or pancreatitis can occur as chronic pancreatitis, which describes pancreatitis that occurs over many years. Symptoms incudes upper abdominal pain, nausea, vomiting, tenderness when touching the abdomen etc.	which are known to be associated with pancreatitis such as increased triglycerides, gallstones, and alcohol consumption. Mild cases of pancreatitis may go away without treatment, but severe cases can cause life-threatening complications. Physician should be advised in case of occurrence of such adverse events.
Bowel obstruction *(Intestinal obstruction)*	Intestinal obstruction is a partial or complete blockage of the bowel that prevents the contents of the intestine from passing through. Signs and symptoms of intestinal obstruction include: crampy abdominal pain that comes and goes, nausea, vomiting, diarrhea, constipation, inability to have a bowel movement or pass gas, swelling of the abdomen (distention). Constipation represents a risk factor for intestinal obstruction. 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.	Because of the serious complications that can be developped from intestinal obstruction (such as yellowing of the skin and eyes), immediate medical advice may be taken if patient have severe abdominal pain or other symptoms of intestinal obstruction.
Change in electrical activity of the heart seen on ECG	The Q-T interval is the section on the electrocardiogram	As with other antipsychotics, caution should be exercised

(QT prolongation)	(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	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.
Blood clot in the veins especially in the legs that travels in the blood *(Venous thromboembolism*)	Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Symptoms include swelling, pain and redness in the leg as well as chest pain and difficulty in breathing.	All possible risk factors for venous thromboembolism (VTE) should be identified before and during treatment with quetiapine and preventive measures undertaken. If patient notice any of VTE symptoms should seek medical advice immediately.
Elevation of diastolic blood pressure in the pediatric population *(Increased blood pressure in the paediatric population)*	Increases in blood pressure have been reported in children and adolescents treated with quetiapine although this adverse event has not be observed to the adults.	This adverse event may affect up to 1 in 10 people. If elevation of diastolic blood pressure occurs, physician should immediately be advised.

Important potential risks	
Risk	**What is known (Including reason why it is considered a potential risk)**
Cerebrovascular adverse effects in elderly patients	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 adverse effects in 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.
Serotonin syndrome	Quetiapine affects a wide range of neurotransmitters, including dopamine and serotonin. Serotonin syndrome can occur when prescribing high doses of a single serotonergic agent, after adding a second serotonergic drug, during switching of antidepressants or when drugs with different mechanisms of increasing serotonin are used together. Symptoms may include: confusion and agitation, hyperreflexia and clonus, flushing, shivering, sweating and hyperthermia. The symptom profile of serotonin syndrome overlaps with neuroleptic malignant syndrome
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.
Sudden death	
Myocarditis	No case reports associating quetiapine treatment with myocarditis have yet been published, but two cases of cardiomyopathy with quetiapine administration are registered in the World Health Organization database
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
Cataract	The development of cataracts was observed in association with quetiapine treatment in chronic dog. Lens changes have also been observed in patients during long-term quetiapine treatment, but a causal relationship to quetiapine use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.
Increased mortality in elderly demented patients	In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo (5.5% versus 3.2 in the group of patient not treated with quetiapine). The patients in these trials died from a variety of causes that were consistent with expectations for this population. These data do not establish a causal relationship between quetiapine treatment and death in elderly patients with dementia.
Aggression/agitation	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.
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.
Accidental injury	Quetiapine treatment has been associated with orthostatic hypotension and related dizziness which, like somnolence has 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.
Aspiration pneumonia	Aspiration pneumonia is bronchopneumonia that develops due to the entrance of foreign materials into the bronchial tree, usually oral or gastric contents (including food, saliva, or nasal secretions). Aspiration pneumonia is often caused by an incompetent swallowing mechanism, such as occurs in some forms of neurological disease or injury. Quetiapine should be used with caution in patients at risk for aspiration pneumonia as difficulty swallowing (dysphagia) has been reported with the drug
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.
Use in patients with hepatic impairment	Quetiapine is extensively metabolized by the liver. Therefore, quetiapine should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.
Use in elderly patients	Quetiapine is not approved for the treatment of dementia-related psychosis in the elderly. As with other antipsychotics and antidepressants, quetiapine should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of quetiapine 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. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient. In elderly patients with major depressive episodes in major depression disorder, dosing should begin with 50 mg/day on Days 1- 3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment. Quetiapine treatment has been associated with orthostatic hypotension and related dizziness that could increase the occurrence of accidental injury (fall), especially in the elderly population. 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.
Treatment emergent mania in bipolar disorder	After successful treatment for an acute depressive episode, patients should not routinely continue on antidepressant treatment long-term, because there is no evidence that this reduces relapse rates, and it may be associated with increased risk of switching to mania.

Missing information	
Risk	**What is known**
Use in patients with renal impairment	No clinically significant differences were found when the pharmacokinetic parameters for subjects with renal or hepatic impairment were compared with those for healthy control subjects. The results indicate that dosage adjustment of quetiapine may be unnecessary in psychotic patients with decreased renal function.
Use in patients with hepatic impairment	Quetiapine therapy should be initiated at 25 milligrams (mg)/day then increased daily in increments of 25 to 50

	mg/day to an effective dose; patients with hepatic impairment have a 30% lower mean oral clearance of quetiapine than subjects with normal hepatic clearance
Use in pregnant or lactating 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 of different racial or ethnic origin	Optimal treatment for patients with mental health illness depends upon accurate diagnosis, individualized treatment, patient adherence to effective agents, and an intact family support system. Furthermore, limited data in African Americans, Hispanics, and Asians suggest that there are racial, ethnic, and cultural variations in responsiveness to antipsychotic medications, as well as potential differences in the types, rates, and severity of adverse events. Non-Caucasian patients tend to receive older, less-expensive agents, sometimes at higher doses (African Americans, leading to potentially intolerable side effects and early withdrawal of therapy or a less than optimal therapeutic response, respectively. Differences in response may have a biologic, pharmacokinetic, or pharmacodynamic basis and may also be influenced by lifestyle factors (eg, diet, smoking). While further research is needed, recognition of potential interracial/ethnic pharmacogenetic differences may help minimize intolerable side effects and achieve optimal psychosis management. However, there is no relative data in the product SmPC
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
Use in patients with longer-term exposure	Long-term efficacy and safety in patients with major depression disorder has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy Quetiapine 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. 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.

VI.2.5 Summary of risk minimisation measures by safety concern

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

Not applicable

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

Version	Date	Safety concerns	Change
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	Implementation of Assessor (day 70 +100) comments Implementation of updated EU template of generic RMP (EMA/465932/2013 Rev.1 of 25 July 2013)

		•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 non-elderly 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	16.09.2014	**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 •Metabolic risk factors •Hyponatraemia and SIADH •Hypothyroidism •Hyperprolactinemia •Anaphylactic reaction •Jaundice, hepatitis,	Day 120 RMS Assessment

		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 non-elderly 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	

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