## VI.2 Elements for a public summary

### VI.2.1 Overview of disease epidemiology

***Major Depressive Disorder (MDD)***

Major depressive episodes consist of a period, during which a drop in interest/pleasure is present for almost every activity or a change from the person's normal mood. This feeling can interfere with daily activities such as taking care of family, spending time with friends, or going to work or school. To be diagnosed as a major depressive episode, at least five of the following symptoms have to persist all the day and to last at least for a couple of weeks:

- Persistent sad, anxious or "empty" mood
- Feelings of hopelessness, pessimism
- Feelings of guilt, worthlessness, helplessness
- Loss of interest or pleasure in hobbies and activities previously considered as interesting, including sex
- Decreased energy, fatigue, feeling "slowed down"
- Difficulty concentrating, remembering, making decisions
- Insomnia, early-morning awakening, or oversleeping
- Low appetite and weight loss or overeating and weight gain
- Thoughts of death or suicide, suicide attempts
- Restlessness, irritability
- Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders and pain for which no other cause can be diagnosed.

Major depressive episodes may occur once or twice in a lifetime, or they may re-occur frequently. They may also take place spontaneously, during or after the death of a loved one, a romantic breakup, a medical illness, or other life events. Some people with major depression may feel that life is not worth living and some will attempt to end their lives.[1]

Causes are still unclear. Most likely, depression is caused by a combination of genetic, biological, environmental, and psychological factors.[2]

***Schizophrenia***

Schizophrenia is a severe brain disorder in which people interpret reality abnormally. In other words, schizophrenia affects how a person thinks, feels and acts. Someone with schizophrenia may have difficulty distinguishing between what is real and what is imaginary; may be unresponsive or withdrawn; and may have difficulty expressing normal emotions in social situations.[3]

The signs of schizophrenia are different for everyone. Symptoms may develop slowly over months or years, or may appear very abruptly. The disease may come and go in cycles of relapse and remission.

Behaviors that are early warning signs of schizophrenia include hearing or seeing something that is not there, a constant feeling of being watched, peculiar or meaningless way of speaking or writing, feeling

[1] Anxiety and Depression Association of America_Depression. Available on http://www.adaa.org/understanding-anxiety/depression. Accessed on 22/05/2015.

[2] US National Institute of Mental Health_Depression – Causes. Available on http://www.nimh.nih.gov/health/topics/depression/index.shtml. Accessed on 22/05/2015.

[3] Mayo Clinic_Diseases and Conditions_ Schizophrenia. Available on http://www.mayoclinic.org/diseases-conditions/schizophrenia/basics/definition/con-20021077. Accessed on 22/05/2015.

indifferent to very important situations deterioration of academic or work performance, a change in personal hygiene and appearance or personality, avoid meeting other people, irrational, angry or fearful response to loved ones, inability to sleep or concentrate, inappropriate or bizarre behaviour.
The cause of schizophrenia is still unclear. Many theories have been formulated along the years. The most substantiated are that a combination of genetics (having a family history of schizophrenia) and environment contributes to development of the disorder. [4]
Other factors seem to increase the risk of developing or triggering schizophrenia, including exposure to viruses, toxins or malnutrition while in the womb, increased immune system activation (for instance from inflammation or autoimmune diseases) older age of the father and taking mind-altering (psychoactive or psychotropic) drugs during teen years and young adulthood.[3]

***Bipolar disorder***

Bipolar disorder is characterized by unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. People with bipolar disorder experience unusually intense emotional states that occur in distinct periods called "mood episodes." Each mood episode represents a drastic change from a person's usual mood and behavior. An overly joyful or overexcited state is called a manic episode, and an extremely sad or hopeless state is called a depressive episode. Sometimes, a mood episode includes symptoms of both mania and depression. This is called a mixed state.
A manic state can be recognized by differents signs and symptoms such as being feeling high/extremely happy and outgoing, being extremely irritable or easily distracted, sleeping little overly restless and not feeling tired, talking very fast, jumping from one idea to another, having an unrealistic belief in one's abilities, acting impulsively (sometimes with dangerous behaviours) increasing activities and setting out to do new projects.
On the contrary, signs and symptoms of depression or a depressive episode include a long period of feeling sad or hopeless and tired, loss of interest in activities once enjoyed including sexual intercourses, encountering difficulties in concentrating, remembering, and making decisions, changing habits like eating (thus losing or gaining weight) or sleeping (over or undersleeping), thinking of death or suicide, or attempting suicide.
Manic or depressive episodes can be sometimes acompanied by psychotic symptoms such as hallucinations (e.g. believing to be a famous person, having a lot of money, or special powers) or delusions (e.g. believing to be ruined and without money, or to have committed a crime). People with bipolar disorder may also abuse alcohol or substances, have relationship problems, or perform poorly in school or at work.
Bipolar disorder usually lasts a lifetime. Episodes of mania and depression typically resolve over time. Between episodes, many people with bipolar disorder are free of symptoms, but some people may have persistant symptoms.[5]

### VI.2.2 Summary of treatment benefits

***Schizophrenia***

[4] Menthal Health America©_Schizophrenia. Available on http://www.mentalhealthamerica.net/conditions/schizophrenia. Accessed on 22/05/2015.
[5] US National Institute of Mental Health_Bipolar Disorder. Available on http://www.nimh.nih.gov/health/topics/bipolar-disorder/index.shtml. Accessed on 22/05/2015.

The efficacy of quietapine extended release tablets (a formulation in which drug is released slowly over time) in the treatment of schizophrenia was tested in two different clinical studies, i.e. research studies in which patients are usually divided in two groups (one taking the experimental drug and the other only an inactive substance also called placebo) with the aim to demonstrate that the experimental drug treatment is effective and safe. Results of the first study showed that quetiapine administered at different doses (400, 600 and 800 mg per day) were associated to significant improvements in psychotic symptoms with a greater effect obtained using higher doses.
Another study, in which patients took quietapine extended release tablets for a long time, revealed that the medicine was more effective than placebo in preventing relapse of symptoms. The risk of relapse was lower also 6 months after the end of the therapy. Long term therapy did not increase drug-related side effects such as movement disorders and weight gain.[6]

***Major Depressive Disorder (MDD)***

Even if approved only as add-on treatment quetiapine extended release tablets were also tested in clinical trials as monotherapy, where was proven to be effective in the treatment of major depressive disorder. It demonstrated superior efficacy to placebo in reducing depressive symptoms as well as in preventing relapse of depressive episodes.
Moreover given as add-on treatment to ongoing antidepressant monotherapy in which patients had shown an inadequate response, it displayed superiority over antidepressant therapy alone, in reducing depressive symptoms.[6]

***Bipolar disorder***

Quetiapine is an atypical antipsychotic with a superior tolerability profile to conventional antipsychotics. Large, placebo-controlled studies have shown the efficacy of quetiapine for treating both acute manic episodes (as monotherapy and combination therapy) and acute depressive episodes (as monotherapy) associated with bipolar disorder.[7]
In particular clinical trials revealed that:

- quetiapine demonstrated superior efficacy compared to placebo in reduction of manic symptoms;
- in treatment of moderate to severe depressive episodes, quetiapine formulation was more effective compared to placebo-treated patients;
- in patients affected by manic, depressed or mixed mood episodes, the combination with quetiapine was superior to lithium or valproate (drug also known as mood stabilizers) monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). In general combined therapy was well tolerated;
- in one long-term study involving patients with bipolar disorder (up to 2 years treatment) quetiapine was superior to placebo in increasing the time in which any mood event (manic, mixed or depressed) presented again.[6]

[6] SmPC for quetiapine prolonged-release tablet, Zentiva
[7] Maria Carolina Hardoy, Alessandra Garofalo, Gisa Mellino, Francesco Tuligi, Mariangela Cadeddu and Mauro Giovanni Carta Quetiapine as add-on treatment for bipolar I disorder: efficacy in preventing relapse of depressive episodes Clinical Practice and Epidemiology in Mental Health 2007, 3:17 doi:10.1186/1745-0179-3-17.

### VI.2.3 Unknowns relating to treatment benefits

***Patients on concomitant cardiovascular medications***

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of quetiapine overdose. Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension.

***Patients on concomitant valproic acid***

Sodium valproate and quetiapine did not interfere significantly 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.

***Pregnant or breastfeeding women***

There is a limited amount of data in pregnant women using quetiapine during the first trimester.These data do not suggest an increased risk of malformations due to treatment. However, animal studies have shown reproductive toxicity. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.
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, increased or diminished muscle tension, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Based on very limited data, excretion of quetiapine into human breast milk when administered at therapeutic doses, appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue quetiapine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### VI.2.4 Summary of safety concerns

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Drug induced movement disorders that results in symptoms as continuous spasms and muscle contractions, motor restlessness, parkinson-like rigidity, slow movements and tremor, and the presence of irregular, jerky movements in the lower face and distal limbs (Extrapyramidal symptoms) | There is a risk of extrapyramidal symptoms onset including tardive dyskinesia (even if lower than other typical antipsychotics) both in adults and in children. In the latter ones they can occur with different implications or higher frequency. | Yes,<br>• By reduction of the dose or discontinuation of the therapy<br>• By close monitoring the patients in order to identify the onset of the first symptoms. |
| Sleepiness (Somnolence) | Quetiapine treatment has been associated in clinical trials with somnolence and sedation usually within the first 3 days of treatment and was mainly of mild to moderate intensity. | Yes,<br>• 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. |
| Weight gain | Weight gain has been seen in patients taking quetiapine. | Yes,<br>• Weight gain should be monitored. Doctor should be contacted if patient notices weight gain. |
| Changes in the amount of certain fats in the blood (Lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs)) | Changes in the amount of certain fats in the blood (increases in triglycerides, LDL and total cholesterol, and decreases in HDL) have been observed in clinical trials with quetiapine. | Yes,<br>• Doctor may order blood tests to monitor changes in the amount of fats in the blood. |

| **Risk** | **What is known** | **Preventability** |
|---|---|---|
| A group of metabolic diseases characterized by high blood sugar concentration resulting from defects in insulin (a hormone produced by pancreas) secretion, insulin action, or both (Hyperglycaemia and diabetes mellitus) | High blood sugar and/ or development or exacerbation of diabetes including some fatal cases, have been reported rarely. Sometimes they were accompanied by a prior increase in body weight which may be a predisposing factor together with family history of diabetes. | Yes,<br>• Doctor should be informed before taking quetiapine if patient has experienced high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite, and feeling weak) or has family history of diabetes.<br>• Patients treated with any antipsychotic agents, including quetiapine, should be observed for signs and symptoms of high blood sugar and patients with diabetes or with risk factors for diabetes should be monitored regularly for worsening of glucose control. |
| Factors increasing the chances of having metabolic syndrome such as high blood pressure, lipid abnormalities, high blood sugar, and excess body weight, particularly at the waistline, race (Metabolic risk factors) | Given the observed changes in body weight, blood sugar and blood fats seen in clinical studies, patients (including those with normal values before quetiapine treatment) may experience worsening of their metabolic risk profile. | Yes,<br>• Monitoring patients for worsening of their metabolic risk profile (changes in body weight, blood sugar and blood fats). |

| **Risk** | **What is known** | **Preventability** |
|---|---|---|
| Specific change in electrical activity of the heart (QT prolongation) | QT prolongation has been reported with quetiapine at the regular doses and in overdose. | Yes,<br>• Before taking quetiapine, patients should inform doctor if they, or someone in their family, has or has had any heart problems such as a very fast heart beat or prolonged QT on an ECG (heart tracing), or if patient uses medicines that have an impact on the way heart beats, for example, medicines that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (water pills) or certain antibiotics (medicines to treat infections). |

**Important potential risks**

| **Risk** | **What is known (Including reason why it is considered a potential risk)** |
|---|---|
| Tendency to commit suicide (Suicide and suicidality) | The risk of suicide related to the depressive state of the patient, may increase in the early stages of recovery since improvement of the psychical condition may not occur during the first few weeks or more of treatment with quetiapine.<br>In addition there is a potential risk of suicide-related events after abrupt cessation of quetiapine treatment. |
| A break of blood supply to the brain in elderly patients affected by decline in mental ability complicated by behavioural and psychological symptoms including restlessness, aggression, delusions, hallucinations, apathy and sleep disturbances. (Cerebrovascular AEs in the elderly) | An approximately 3-fold increased risk of cerebrovascular adverse events has been seen during clinical studies in which the dementia population was treated with the class of medicines to which quetiapine belongs. The mechanism for this increased risk is not known. |
| A break of blood supply to the brain in non-elderly patients affected by decline in mental | An approximately 3-fold increased risk of cerebrovascular adverse events has been seen during clinical studies in which the dementia population was treated with the class of medicines to which |

| **Risk** | **What is known (Including reason why it is considered a potential risk)** |
|---|---|
| ability complicated by behavioural and psychological symptoms including restlessness, aggression, delusions, hallucinations, apathy and sleep disturbances. (Cerebrovascular AEs in the non-elderly patients) | quetiapine belongs. The mechanism for this increased risk is not known. Similar increase of risk in other patient groups have not been excluded. |
| Certain heart rhythm disorder (Torsades de Pointes) | The class of medicines to which quetiapine belongs can cause heart rhythm problems, which can be serious and in severe cases may be fatal. |
| Heart disease characterized by reduced blood supply to the heart (Ischemic heart disease) | Quetiapine should be used with caution in patients with known heart disease since quetiapine has effects on blood pressure. |
| Drug deliberately used by the patient for non-therapeutical purposes or not according to indication and doses reported in information leaflet (Abuse and misuse) | Such as other medicinal products affecting central nervous sytem, quetiapine has potential for abuse and misuse if product information regarding indications and posology are not followed. |
| Drug prescribed by the doctor not according to indication and/or route of administration and/or doses reported in the information leaflet and wrong dose of drug administered to/taken by the patient (Potential for off label use and misdosing) | Such as other medicinal products, quetiapine has potential for off-label use and misdosing if product information regarding indications and posology are not followed. |

**Important missing information**

| **Risk** | **What is known** |
|---|---|
| Limited information on use during pregnancy and breastfeeding (Use in pregnant or breast feeding women) | The moderate amount of published data from pregnant women exposed during the first trimester do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.<br>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, increased or diminished muscle tension, tremor, somnolence, respiratory distress, or feeding disorder. |

| **Risk** | **What is known** |
|---|---|
| | Consequently, newborns should be monitored carefully.<br>Based on very limited data excretion of quetiapine into human breast milk when administered at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue quetiapine therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. |
| Limited information on use in patients under concomitant therapy with a medication used to treat diseases affecting hearth and/or vessels (Use in patients on concomitant cardiovascular medications) | Formal interaction studies with commonly used cardiovascular medicinal products have not been performed. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of quetiapine overdose. Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to low blood pressure. |
| Limited information on use in patients under concomitant therapy with a medication (valproic acid) primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches (Use in patients on concomitant valproic acid) | Sodium valproate and quetiapine did not interact significantly when co-administered. A 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. |

### VI.2.5 Summary of risk minimisation measures by safety concern

These additional risk minimisation measures are for the following risks:

**EXTRAPYRAMIDAL SYMPTOMS**

| **Risk minimisation measure(s): Healthcare professional educational materials** |
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| **Objective and rationale:** To inform HCP about the identified risk of extrapyramidal symptoms (movement disorders that results in symptoms as continuous spasms and muscle contractions, motor restlessness, parkinson-like rigidity, slow movements and tremor, and the presence of irregular, jerky movements in the lower face and distal limbs) in patient treated with quetiapine and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. |
| The applicant will ensure that all physicians, prescribing quetiapine prolonged-release tablets (50, 150, 200, 300, 400 mg), have at their disposal educational materials to help instruct patients, their families and caregivers on the key messages regarding the safety profile of quetiapine with respect to extrapyramidal symptoms:<br>• Patients should be instructed on what extrapyramidal symptoms are and carefully monitored during therapy with quetiapine.<br>• Treatment with quetiapine should be started at a low dose and increased gradually to an effective dose as the risk of developing extrapyramidal symptoms and the probability that they will become irreversible are directly related to the duration of treatment and the total dose of medication administered over time.<br>• Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal symptoms that may vary in severity and duration following delivery. Consequently, newborns should be monitored carefully.<br>• In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory response should be prescribed.<br>• If during treatment with quetiapine involuntary, repetitive body movements appears, drug discontinuation should be considered. However, some patients may require treatment with quetiapine despite the presence of these symptmos. |

**SOMNOLENCE**

| **Risk minimisation measure(s): Healthcare professional educational materials** |
|---|
| **Objective and rationale:** To inform HCP about the identified risk of somnolence (sleepiness) in patient treated with quetiapine and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. |
| The applicant will ensure that all physicians, prescribing quetiapine prolonged-release tablets (50, 150, 200, 300, 400 mg), have at their disposal educational materials to help instruct patients, their families and caregivers on the key messages regarding the safety profile of quetiapine with respect to somnolence:<br>• Quetiapine treatment has been associated with somnolence of mild to moderate intensity and related symptoms, such as sedation. Somnolence is a commonly reported adverse reaction in patients treated with quetiapine, especially during the first three days of therapy.<br>• Patients should be advised about the risk of somnolence or sedation (which may lead to falls especially in the elderly population). Patients should be cautioned about performing any activity requiring mental alertness (such as driving a car), until they are reasonably certain quetiapine therapy does not affect them adversely. |

**WEIGHT GAIN**

| **Risk minimisation measure(s): Healthcare professional educational materials** |
|---|
| **Objective and rationale:** To inform HCP about the identified risk of weight gain in patient treated with quetiapine and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. |
| The applicant will ensure that all physicians, prescribing quetiapine prolonged-release tablets (50, 150, 200, 300, 400 mg), have at their disposal educational materials to help instruct patients, their families and caregivers on the key messages regarding the safety profile of quetiapine with respect to weight gain:<br>• Certain antipsychotic (including quetiapine) medications increase appetite and this leads to put on fat. Weight gain has been reported in patients who have been treated with quetiapine.<br>• Patients' weight should be regularly checked. |

**LIPID CHANGES (increased cholesterol, increased triglycerides, or decreased HDLs)**

| **Risk minimisation measure(s): Healthcare professional educational materials** |
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| **Objective and rationale:** To inform HCP about the identified risk of lipid changes (changes in the amount of certain fats in the blood) in patient treated with quetiapine and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. |
| The applicant will ensure that all physicians, prescribing quetiapine prolonged-release tablets (50, 150, 200, 300, 400 mg), have at their disposal educational materials to help instruct patients, their families and caregivers on the key messages regarding the safety profile of quetiapine with respect to lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs):<br>• Patients that during treatment with quetiapine might experience an increase in total cholesterol, LDL-cholesterol (the so-called bad cholesterol) and triglycerides and decreases in HDL-cholesterol (the so-called good cholesterol).<br>• The physical wellbeing of all patients should be identified as early as possible, monitored, and treated according to relevant clinical guidelines.<br>• Patients' blood lipids should be regularly checked. |

**HYPERGLYCEMIA AND DIABETES MELLITUS**

| **Risk minimisation measure(s): Healthcare professional educational materials** |
|---|
| **Objective and rationale:** To inform HCP about the identified risk of hyperglycemia and diabetes mellitus (a group of metabolic diseases characterized by high blood sugar concentration resulting from defects in insulin (a hormone produced by pancreas) secretion, insulin action, or both) in patient treated with quetiapine and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. |
| The applicant will ensure that all physicians, prescribing quetiapine prolonged-release tablets (50, 150, 200, 300, 400 mg), have at their disposal educational materials to help instruct patients, their families and caregivers on the key messages regarding the safety profile of quetiapine with respect to hyperglycemia and diabetes mellitus:<br><br>• Patients, family members, and caregivers should be aware of the signs and symptoms of diabetes and especially those associated with the acute decompensation of diabetes (i.e.blood sugar levels cannot be corrected by means of drugs) such as diabetic ketoacidosis characterised by a rapid onset of: polyuria (large production of urine), polydipsia (excessive thirst), weight loss, nausea, vomiting, dehydration (loss of body water), rapid respiration and inability to think, even coma. The latter is a life-threatening condition and always requires immediate treatment. |

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| • Patients' blood lipids should be regularly checked. |

**METABOLIC RISK FACTORS**

| **Risk minimisation measure(s): Healthcare professional educational materials** |
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| **Objective and rationale:** To inform HCP about the increased rates of metabolic disorders in patients treated with quetiapine and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. |
| The applicant will ensure that all physicians, prescribing quetiapine prolonged-release tablets (50, 150, 200, 300, 400 mg), have at their disposal educational materials to help instruct patients, their families and caregivers on the key messages regarding the safety profile of quetiapine with respect to metabolic risk factors:<br>• People with schizophrenia or bipolar disorder have increased rates of metabolic disorders and are more likely to die prematurely from natural causes (mainly cardiovascular diseases) compared with people without mental health disorders. Treatment with antipsychotic drugs can cause or aggravate these disorders. Schizophrenia also seems to be associated with modifiable and non- modifiable risk factors for cardiovascular morbidity and mortality (e.g. smoking, poor diet, sedentary lifestyle, and family history of cardiovascular disease).<br>• Metabolic risk factors associated with major mental illness among patients taking quetiapine include:<br>- Overweight/obesity;<br>- Smoking;<br>- Lack of physical activity;<br>- Poor dietary habits;<br>- Increased risk of<br>º Diabetes mellitus;<br>º Dyslipidemia (an abnormal amount of lipids (e.g.,triglycerides, cholesterol) in the blood).<br>• The physical wellbeing of all patients should be assessed, monitored, and treated according to relevant clinical guidelines. |

**POTENTIAL FOR OFF LABEL USE AND MISDOSING**

| **Risk minimisation measure(s): Healthcare professional educational materials** |
|---|
| **Objective and rationale:** To inform HCP about the potential risk of off label use (drug prescribed by the doctor not according to indication and/or route of administration and/or doses reported in the information leaflet) and misdosing (wrong dose of drug administered to/taken by the patient) in patients treated with quetiapine and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity. |
| The applicant will ensure that all physicians, prescribing quetiapine prolonged-release tablets (50, 150, 200, 300, 400 mg), have at their disposal educational materials to help instruct patients, their families and caregivers on the key messages regarding the safety profile of quetiapine with respect to metabolic risk factors:<br>• Psychiatric medicines are among the most common drugs to be prescribed off-label, and their use in children is of special concern. Atypical antipsychotics such as quetiapine have been studied as off-label treatment for many conditions including eating disorders, personality disorders, substance abuse and insomnia. However, it has been demonstrated that atypical antipsychotics were not effective in the treatment of eating disorders or personality disorder or in the cases where a beneficial effect was evident the size of the effect was very small. The evidence did not even support the use of atypical antipsychotics in the treatment of substance abuse, |

and data were inconclusive for the use of these medications for insomnia. For these reasons and since it is well known that quetiapine, expecially when used used chronically, can cause adverse reactions such as movement disorders and metabolic complications, use of quetiapine not according the product information leaflet is not recommended.

- There are different dosing schedules according to the different indications reported in the information leaflet. Patients must receive clear information on the appropriate dosage for their condition. Tablets should be administered once daily, without food. They should be swallowed whole and not split, chewed or crushed.

### 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 | Comment |
|---|---|---|---|
| 1.0 | 25/05/2014 | **Important identified risks:**<br>• Extrapyramidal symptoms, including tardive dyskinesia<br>• Severe neutropenia and agranulocytosis<br>• Neuroleptic malignant syndrome<br><br>**Important potential risks:**<br>• Suicidal behaviour<br>• Hyperglycaemia and diabetes mellitus<br>• Orthostatic hypotension<br>• Cardiac arrhythmias (QT prolongation)<br>• Cerebrovascular events in elderly patients with dementia-related psychosis<br><br>**Important missing information:**<br>• Safety in paediatric population below 18 years of age<br>• Safety in patients over 65 years<br>• Safety in pregnancy and lactation<br>• Effects on fertility | Initial version. |
| 1.1 | 21/10/2015 | **Important identified risks:**<br><br>• Extrapyramidal symptoms, including tardive dyskinesia<br>• Neutropenia<br>• Agranulocytosis<br>• Neuroleptic malignant syndrome<br>• Somnolence<br>• Syncope and orthostatic hypotension<br>• Seizures<br>• Weight gain<br>• Lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs)<br>• Hyperglycemia and diabetes mellitus<br>• Metabolic risk factors<br>• Hyponatraemia and SIADH<br>• Hypothyroidism<br>• Hyperprolactinemia | The RMP was updated according to DHMA (Danish NCA acting as RMS) request to update RMP safety specification and to implement additional risk minimization measures in the form of health care professional educational materials in line with RMP for the reference product Seroquel. |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | • Anaphylactic reaction<br>• Hepatitis with or without jaundice<br>• Stevens-Johnson syndrome<br>• Withdrawal (discontinuations) symptoms and neonatal withdrawal<br>• Dysphagia<br>• Pancreatitis<br>• Intestinal obstruction<br>• QT prolongation<br>• Venous thromboembolism<br>• Increased blood pressure in the pediatric patient population<br><br>**Important potential risks:**<br><br>• Suicide and suicidality<br>• Cerebrovascular events in elderly patients<br>• Cerebrovascular AEs in the non-elderly patients<br>• Torsades de pointes<br>• Ischemic heart disease<br>• Increased mortality in elderly demented patients<br>• Aggression/agitation<br>• Abuse and misuse<br>• Accidental injury<br>• Aspiration pneumonia<br>• Potential for off label and misdosing<br>• Use in elderly patients<br><br>**Important missing information:**<br><br>• Pregnant or breastfeeding women<br>• Patients on concomitant cardiovascular medications<br>• Patients on concomitant valproic acid<br>_____<br><br>**Additional risk minimisation measures** for the following safety concerns:<br><br>• Extrapyramidal symptoms<br>• Somnolence<br>• Weight gain<br>• Lipid changes (increased | |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | cholesterol, increased triglycerides, or decreased HDLs)<br>• Hyperglycemia and diabetes mellitus<br>• Metabolic risk factors | |
| 1.2 | 02/03/2016 | **Important identified risks:**<br><br>• Extrapyramidal symptoms<br>• Somnolence<br>• Weight gain<br>• Lipid changes (increased cholesterol, increased triglycerides, or decreased HDLs)<br>• Hyperglycemia and diabetes mellitus<br>• Metabolic risk factors<br>• QT prolongation<br><br>**Important potential risks:**<br><br>• Suicide and suicidality<br>• Cerebrovascular AEs in the elderly<br>• Cerebrovascular AEs in the non-elderly patients<br>• Torsades de pointes<br>• Ischemic heart disease<br>• Abuse and misuse<br>• Potential for off label use and misdosing<br><br>**Important missing information:**<br><br>• Use in pregnant or breast feeding women<br>• Use in patients on concomitant cardiovascular medications<br>• Use in patients on concomitant valproic acid<br><br>_____<br><br>**Additional risk minimisation measures** for the following safety concerns:<br><br>• Extrapyramidal symptoms<br>• Somnolence<br>• Weight gain<br>• Lipid changes (increased | The RMP was updated according to DHMA (Danish NCA acting as RMS) request to update RMP safety specification and additional risk minimization measures in line with RMP for the reference product Seroquel (RMP for the originator product was under review at the time of Day 70 assessment report concerning Quetiapine Zentiva). |

| Version | Date | Safety Concerns | Comment |
|---|---|---|---|
| | | cholesterol, increased triglycerides, or decreased HDLs)<br>• Hyperglycemia and diabetes mellitus<br>• Metabolic risk factors<br>• Potential for off label use and misdosing | |