VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Schizophrenia:

Schizophrenia is a severe mental illness that has a number of symptoms including disorganized thinking and speech, hallucinations (hearing or seeing things that are not there), suspiciousness and delusions (mistaken beliefs), that typically appears in adulthood. Men and women are affected equally though symptoms appear slightly earlier in men than in women. In Europe about 15 in every 100,000 people (0.015%) are newly diagnosed with schizophrenia each year, and it is thought that about 1 in every 100 people (1%) have the disease at any one time.

Bipolar disorder:

Bipolar I disorder is a serious medical illness that causes shifts in mood, energy, and ability to function. Twelve-month occurrence of bipolar I disorder across the world ranged from 0.0% to 0.6%. The lifetime male-to-female occurrence ratio is approximately 1.1:1. Mean age is approximately 18 years for bipolar I disorder. Bipolar disorder is more common in high-income than in low-income countries. Separated, divorced, or widowed individuals have higher rates of bipolar I disorder than do individuals who are married or have never been married. There is an average 10-fold increased risk among adult relatives of individuals with bipolar I and bipolar II disorders. Metabolic syndrome and migraine are more common among individuals with bipolar disorder than in the general population. More than half of individuals with bipolar disorder have an alcohol use disorder, and those with both disorders are at greater risk for suicide attempt.

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

An overall population of depressive disorders has been reported as 1 in 10 in Europe. These figures can be subdivided to show that the frequency of depression occurring in women was 1 in 10 and 1 in 15 for men. Functional impairment was associated with recency of MDE(Major Depressive Episodes). The female: male ratio was about 2:1. In high-income countries, younger age was associated with higher 12-month prevalence; by contrast, in several low- to middle-income countries, older age was associated with greater likelihood of MDE. MDD is currently treated with antidepressants, such as SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin norepinephrine reuptake inhibitors). However, these treatments do not always fully satisfy the needs of patients or physicians. Studies have shown at least one-third of patients fail to achieve a satisfactory response and cause side effects with such antidepressants, even after two to three rounds of therapy hence quetiapine has been used as add-on treatment of major

depressive episodes in patients with MDD. MDE is a significant public-health concern across all regions of the world and is strongly linked to social conditions.

VI.2.2 Summary of treatment benefits

Quetiapine is an antipsychotic medicine which is used to treat schizophrenia (where you may hear or feel things that are not there, believe things that are not true or feel unusually suspicious, anxious, confused, guilty, tense or depressed), mania (where you may feel very excited, elated, agitated, enthusiastic or hyperactive or have poor judgment including being aggressive or disruptive), bipolar depression and major depressive episodes in major depressive disorder (where you may feel sad all the time or you may find that you feel depressed, feel guilty, lack energy, lose your appetite or can't sleep).

Schizophrenia:

The effectiveness of quetiapine in the treatment of schizophrenia was demonstrated in patients who met DSM-IV criteria (measuring criteria for mental illness) for schizophrenia. Quetiapine 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. In patients stabilised on Quetiapine immediate-release tablet 400 mg to 800 mg, effectiveness was maintained when patients were switched to an equivalent daily dose of quetiapine given once daily.

Bipolar Disorder:

In the treatment of moderate to severe manic episodes, quetiapine demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy studies.

Major depressive episodes in MDD <u>in patient who had sub-optimal response to antidepressant monotherapy:</u>

Quetiapine prolonged-release tablets 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine. The result demonstrated good response over antidepressant therapy alone in reducing depressive symptoms.

VI.2.3 Unknowns relating to treatment benefits

The safety and effectiveness of quetiapine has not been studied in pregnant and breast feeding women, patients of different or certain ethnic or racial origin, patient on concomitant cardiovascular medication or valproic acid and long-term exposure and malignancies.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Increase in the level of sugar in blood (Hyperglycaemia and diabetes)	People taking quetiapine commonly (may affect less than 1 in 10 patient) developed high blood sugar. People taking quetiapine commonly (may affect up to 1 in 100 patients) developed worsening of pre-existing diabetes. Some side effect like sugar in blood is only seen when a blood test is taken. An excess of glucose in bloodstream and/or development or exacerbation of diabetes (high blood glucose, either because insulin production is inadequate, or because body cell do not respond properly to insulin) occasionally associated with high concentration of ketone bodies or coma has been reported rarely, including some death cases.	You should inform your doctor in case you have diabetes or is at a risk of getting diabetes. The doctor may check your blood sugar levels while you are on treatment with quetiapine. Doctor may ask you to have blood tests from time to time.

Decreases in thyroid hormone levels (Hypothyroidism)	People taking quetiapine uncommonly (affects 1 in 100 patients) developed decreases in thyroid hormone levels. Some side effect like changes in the amount of thyroid hormones in the blood is only seen when a blood test is taken. Changes in thyroid function tests have also been observed in children and adolescents.	If you have thyroid disorder, please tell to your doctor. Your doctor may check your blood thyroid hormone levels while you are on quetiapine treatment.

Risk	**What is known**	**Preventability**
Increased blood pressure in paediatric population	People (children and adolescents) taking quetiapine very commonly (may affect more than 1 in 10 people) experienced increased blood pressure.	You should inform to your doctor if you or your child who are on quetiapine therapy and experienced increase in blood pressure.
Severe reduction in the number of white blood cells (Agranulocytosis)	People taking quetiapine rarely (may affect up to 1 in 1000 patients) experienced severe reduction in the number of white blood cells (agranulocytosis).	Yes, You have or had low levels of white blood cells in the past (which may or may not have been caused by other medicines) you should inform to your doctor before taking quetiapine.

Change in electrical activity of the heart seen on ECG (QT prolongation)	People taking quetiapine uncommonly (affect 1 in 100 patients) experienced change in electrical activity of the heart seen on ECG (QT prolongation). QT prolongation was reported when people receiving quetiapine therapeutic doses and quetiapine overdose.	Before you take the medicine, you should inform to your doctor if you, or someone in your family have or had any heart problems such as a very fast heart beat or prolonged QT on an ECG (heart tracing), or if you are taking any medicines that may have an impact on the way your heart beats. If you notice this side effect, please tell your doctor or pharmacist.

Metabolic risk factors	People taking quetiapine very rarely (affect less than 1 in 10,000 patients) experienced metabolic syndrome. Weight gain has been seen in patients taking quetiapine. Quetiapine can cause changes in the amount of certain fats (triglycerides and total cholesterol) or sugar in the blood, decreases in the number of certain types of blood cells, decrease in the amount of sodium in the blood and increases in the amount of the hormone prolactin in the blood	Your doctor will do weight measurement and blood tests at regular interval while you are on quetiapine treatment.

Obstruction of a blood vessel by a blood clot (Venous thromboembolism)	People taking quetiapine rarely (affect less than 1 in 1,000 patients) cause blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing.	Before you take the medicine, inform to your doctor if you or someone in your family have or had any history of blood clots, as medicines like quetiapine have been associated with formation of

Risk	**What is known**	**Preventability**
Inflammation of pancreas (Pancreatitis)	Patient taking quetiapine rarely (affect less than 1 to 1,000 patients) experienced inflammation of pancreas which causes severe pain in the abdomen and back.	During your treatment with quetiapine if you experienced severe pain in the abdomen and back, fever, nausea and vomiting, you should contact your doctor or pharmacist immediately as these are symptoms of inflammation of pancreas.

Movement disorders caused by abnormalities in the part of the brain that coordinates movement (Extrapyramidal symptoms)	Patient taking quetiapine very commonly (affect more than 1 to 10 patients) experienced abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain. These symptoms occurred at a higher frequency in children and adolescents compared to adults. Neonates exposed to Quetiapine during the third trimester of pregnancy are at risk of shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems and difficulty in feeding that may vary in severity and duration following delivery. Consequently, newborns should be monitored carefully.	If your baby develops shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems and difficulty in feeding you may need to contact his/her doctor.

Involuntary movements of the face and jaw (Tardive dyskinesia)	People taking quetiapine uncommonly (affect 1 in 100 patients) experienced uncontrollable movements, mainly of your face or tongue (Tardive dyskinesia).	Inform your doctor if you experience uncontrollable movements, mainly of your face or tongue.

Sleepiness (Somnolence)	People taking quetiapine very commonly (affect more than 1 in 10 patients) feeling sleepy (this may go away with time, as you keep taking Quetiapine Tablets) (may lead to falls).	Inform your doctor if you feeling of severe sleepiness. This could increase the risk of accidental injury (fall) in elderly patients. Tell your doctor if you are taking barbiturates (for difficulty sleeping). Be careful how much alcohol you drink. This is because the combined effect of quetiapine tables and alcohol can make you feel sleepy. If you take more Quetiapine tablets than prescribed by your doctor, you may experience sleepiness.

Risk	**What is known**	**Preventability**
Fainting and low blood pressure that happens when you stand up from sitting or lying down (Syncope and orthostatic hypotension)	People taking quetiapine very commonly (affect more than 1 in 10 patients) experienced low blood pressure when standing up. This may make you feel dizzy or faint (may led to falls) People taking quetiapine uncommonly (affect 1 in 100 patients) experienced fainting (may lead to falls). People taking quetiapine uncommonly (affect 1 in 100 patients) experienced a slower than normal heart rate which may occur when starting treatment and which may be associated with low blood pressure and fainting.	Before you take quetiapine, tell your doctor if you have low blood pressure. Contact your doctor if you experience any symptoms of decrease in blood pressure during the treatment.
Seizure	People taking quetiapine uncommonly (affect 1 in 100 patients) experienced fits or seizures.	Before you take quetiapine, tell your doctor if you have ever had a fit (seizure). Inform your doctor if you experience fits (seizures) during treatment.

Risk	**What is known**	**Preventability**
Abnormally low count of neutrophils (Neutropenia)	In one study, severe neutropenia (neutrophil count <0.5 X 10^9/L) has been uncommonly reported with quetiapine tablets. Cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine tablets. People taking quetiapine very commonly (affect less than 1 in 10 patients) developed decreased neutrophil count.	During the treatment with quetiapine, your doctor may ask for your blood test to measure neutrophil count Your doctor may discontinue the treatment if neutrophil count <1.0 X 10^9/L.
Weight gain	People taking quetiapine very commonly (affect more than 1 in 10 patients) putting on weight.	If you taking quetiapine, you and your doctor should check your weight regularly. Inform your doctor if you putting on weight.
Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased	People taking quetiapine very commonly (may affect more than 1 in 10 patients) experienced side effect like	During the treatment with quetiapine your lipid has been change, you should contact your doctor or pharmacist

Risk	**What is known**	**Preventability**
HDLs)	changes in the amount of certain fats (triglycerides and total cholesterol) is only seen when a blood test is taken. Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed with quetiapine. In some patients, a worsening of more than one of the metabolic factors of lipids was observed in clinical studies.	immediately. During the treatment with quetiapine, your doctor may ask for blood test to measure lipid level and for actual observation and treatment.
Abnormally high levels of prolactin in the blood (Hyperprolactinaemia)	People taking quetiapine commonly (may affect up to 1 in 10 patients) increases in the amount of hormone call prolactin in the blood. Increasing amount of hormone call prolactin in rare cases can lead to the following: - Swelling of the breasts and unexpected lactation in boys and girls. - The absence or irregularity of menstruation in girls.	If you taking quetiapine, your doctor should check your prolactin level regularly.

Risk	What is known	Preventability
	Elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients. Some side effect like increases in the amount of the hormone prolactin in the blood is only seen when a blood test is taken.	
Allergic reaction (Anaphylactic reaction)	People taking quetiapine uncommonly (affect 1 in 100 patients) experienced allergic reactions that may include raised lumps (weals), swelling of the skin and swelling around the mouth. People taking quetiapine very rarely (affect less than 1 in 10,000 patients) experienced severe allergic reaction (called anaphylaxis) that may include difficulty in breathing, dizziness and collapse.	Do not take Quetiapine Tablets if you are allergic (hypersensitive) to quetiapine or any of the ingredients of quetiapine tablets.

Risk	**What is known**	**Preventability**
Inflammation of the liver (hepatitis), yellowing of the skin and eyes (Jaundice) and increased liver enzyme (serum transaminase and gamma-glutamyl transpeptidase (GGT))	People taking quetiapine rarely (affect less than 1 in 1,000 patients) experienced hepatitis (inflammation of the liver) and jaundice (yellowing of the skin and eyes). Some side effect such as “increased liver enzymes” is only seen when a blood test is carried out.	Before you take your medicine, inform your doctor if you have problems with your liver. Your doctor may start your treatment on a lower dose and increase the dose slowly if you have liver problems.
A form of toxic epidermal necrolysis, in which cell death causes the epidermis to separate from the dermis (Stevens johnson syndrome)	People taking quetiapine very rarely (affect less than 1 in 10,000 patients) developed a severe rash, which may develop quickly. Symptoms may include redness, blistering or peeling of the skin, with possible blisters in the mouth or nose.	Contact your doctor if you experience a form of toxic epidermal necrolysis, in which cell death causes the epidermis to separate from the dermis.
Neurological disorder most often caused by an adverse reaction to neuroleptic or antipsychotic drugs (Neuroleptic malignant syndrome)	People taking quetiapine rarely (affect less than 1 in 1,000 patients) experienced a combination of high temperature (fever), sweating, stiff muscles, feeling very	Inform your doctor if you experience a combination of high temperature (fever), severe muscle stiffiness, feeling confused, sweating or a lowered level of

Risk	What is known	Preventability
	drowsy or faint, large increase in blood pressure or heartbeat (a disorder called “neuroleptic malignant syndrome”).	consciousness (a disorder called “neuroleptic malignant syndrome”). Immediate medical treatment may be needed.
Withdrawal (discontinuation) symptoms and neonatal withdrawal	People very commonly (affect more than 1 in 10 patients) experienced discontinuation symptoms (symptoms which occur when you stop taking quetiapine) include not being able to sleep (insomnia), feeling sick (nausea), headache, diarrhoea, being sick (vomiting), dizziness and irritability. Neonates exposed third trimester of pregnancy are at risk of adverse reactions including withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of risk of shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing	Your doctors will gradually withdrawal the quetiapine over a period of at least 1 to 2 weeks.

Risk	What is known	Preventability
	problems and difficulty in feeding. Consequently, newborns should be monitored carefully.	
Difficulty in swallowing (Dysphagia)	People taking quetiapine uncommonly (affect 1 in 100 patients) experienced difficulty in swallowing.	Swallow the tablets whole with water.
Blockage of small or large intestine (Intestinal obstruction)	People taking quetiapine rarely (may affect up to 1 in 1,000 people) blockage of the bowel.	Inform your doctor as soon as possible if you have constipation along with persistent abdominal pain, or constipation which has not responded to treatment, as this may lead to a more serious blockage of the bowel.
Decrease in the amount of sodium in the blood and inappropriate secretion of a hormone that controls urine volume (Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH))	People taking quetiapine uncommonly (affect 1 in 100 patients) experienced decrease in the amount of sodium in the blood. People taking quetiapine very rarely (may affect up to 1 in 10,000 people) experienced inappropriate secretion of a hormone that controls urine	Some side effects such as “decrease in the amount of sodium in the blood” is only seen when a blood test is carried out. During the treatment with quetiapine, your doctor may ask for blood test to measure sodium level. Contact your doctor if you

Risk	What is known	Preventability
	volume.	have developed inappropriate secretion of a hormone that controls your urine volume.

Important potential risks

Risk	What is known
Safety in elderly patients	**Before you take your medicine, tell your doctor if:** - You have had a stroke, especially if you are elderly. - You are an elderly person with dementia (loss of brain function). If you are, Quetiapine should not be taken because the group of medicines that Quetiapine belongs to may increase the risk of stroke or in some cases the risk of death, in elderly people with dementia. **Tell your doctor immediately if you experience:** - Dizziness or a sever sense of feeling sleepy. This could increase the risk of accidental injury (fall) in elderly patients. **Elderly people** If you have liver problems your doctor may change your dose.
A group of conditions that affect the circulation of blood to the brain in elderly patient (Cerebrovascular adverse	Quetiapine should be used with caution in patients with risk factors for stroke (interrupted blood supply to the brain leading to loss of brain function), especially if you are elderly. Before taking quetiapine, doctor should be informed if the

Risk	**What is known**
effects in elderly patients)	patient is an elderly person with dementia (loss of brain function), if quetiapine should not be taken because the group of medicines that quetiapine belongs to may increase the risk of stroke, or in some cases the risk of death, in elderly people with dementia.
A group of conditions that affect the circulation of blood to the brain in non-elderly patient (Cerebrovascular adverse effects in non-elderly patients)	Quetiapine should be used with caution in patients with risk factors for stroke (interrupted blood supply to the brain leading to loss of brain function). Before taking quetiapine, doctor should be informed if you have any heart disease.
Chest pain or discomfort that occurs when a part of the heart does not receive enough blood. (Ischaemic heart disease)	Quetiapine should be used with caution in patients with known heart disease. Before taking quetiapine, doctor should be informed if the patient or someone in family has or have had any heart problems. If you notice chest pain, chest pressure, or shortness of breath seek medical advice immediately. Ischemic heart disease can be life threatening. Seek immediate medical advice if you, or someone you are with, have any of these life-threatening symptoms including: • Chest pain, typically on the left side of the body (angina pectoris) • Clammy skin • Nausea with or without vomiting • Pain in the neck or jaw

Risk	**What is known**
	• Rapid breathing (tachypnea) or shortness of breath • Shoulder or arm pain
Excessive verbal and/or motor behavior (Aggression/ agitation)	Agitation may occur in newborn babies of mothers that have used quetiapine tablets in the last trimester (last three months of their pregnancy). If your baby develops agitation you may need to contact your doctor.
Suicide and suicidality	If you are depressed you may sometimes have thoughts of harming or killing yourself. These may be increased when first starting treatment, since these medicines all take time to work, usually about two weeks but sometimes longer. You may be more likely to think like this if you are a young adult. Information from clinical trials has shown an increased risk of suicidal thoughts and/or suicidal behaviour in young adults aged less than 25 years with depression. If you have thoughts of harming or killing yourself at any time, contact your doctor or go to a hospital straight away. You may find it helpful to tell a relative or close friend that you are depressed, and ask them to read package leaflet. You might ask them to tell you if they think your depression is getting worse, or if they are worried about changes in your behaviour.
Inflammation of lungs and bronchial tubes (Aspiration pneumonia)	Quetiapine can cause difficult in swallowing. Quetiapine should be used with caution in patients at risk for aspiration pneumonia. Aspiration pneumonia occurs when food, saliva, liquids, or

Risk	**What is known**
	vomit is breathed into the lungs or airways leading to the lungs**.**
Potential for off-label use and misdosing	There were a potential for off-label use and misdosing of quetiapine because quetiapine is given for multiple indications with differing posologies which may increase the chance of error. Always take quetiapine exactly as your doctor has told you.As different dosing schedules exist for each indication, it must therefore be ensured that patients receive clear information on the appropriate dosage for their condition.
Life-threatening irregular heart beat (Torsade de pointes)	Quetiapine tablets can cause heart rhythm problems, which can be serious and in severe cases may be fatal. Before you take quetiapine, tell your doctor if you, or someone in your family have or had any heart problems such as a very fast heart beat or prolonged QT on an ECG (heart tracing), or if you are taking any medicines that may have an impact on the way your heart beats. Tell your doctor if you are taking medicines that affect the heart.
Increased mortality in elderly demented patients	Quetiapine should not be taken by elderly people with dementia (loss of brain function). Quetiapine may increase the risk of stroke or in some cases the risk of death, in elderly people with dementia.
Abuse and misuse	As per Pharmacovigilance Risk Assessment Committee (PRAC) Minutes of the meeting, dated 05-08 May 2014, information on the suspected cases reported and literature data suggested there might be a unexpected risk between abuse in

Risk	What is known
	poly-drug users - who may use quetiapine to reduced effect of other substances that are used and drug-seeking behaviour and in patients with mental distrubance who was seeking a higher dose of quetiapine for its sedative (sleep-inducing) effects to reduce symptoms of insomnia (inability to sleep) and agitation (a state of anxiety).
Accidental injury	Tell your doctor if you feel severe sleepiness and this could increase the risk of accidental injury (fall) in elderly patients. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.
Concomitant use of valproic acid	Effect of sodium valproate and quetiapine were not altered to clinically relevant extent when taken together. In a clinical study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia (decrease in the number of total white blood cells found in blood) and neutropenia (abnormally low concentration of neutrophils in the blood) in the combination group versus the monotherapy groups.

Missing information

Risk	What is known
Safety in pregnant or breastfeeding women	If you are pregnant, trying to get pregnant, or breast-feeding, talk to your doctor or pharmacist before taking Quetiapine. You should not take Quetiapine during pregnancy unless this

Risk	What is known
	has been discussed with your doctor. Quetiapine should not be taken if you are breast-feeding. The following symptoms may occur in newborn babies, of mothers that have used Quetiapine in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
Safety in patient on concomitant cardiovascular medications	Tell your doctor if you are taking any medicines that have an impact on the way your heart beats, for example, drugs that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (water pills) or certain antibiotics (drugs to treat infections).

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) 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). Full details on these conditions can be found in Annex 10 and 11 of this RMP; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities. These additional risk minimisation measures are for the following risks:

- Metabolic risk factors
- Extrapyramidal symptoms
- Somnolence and
- Potential for off-label use and misdosing
- Weight gain

- Lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs)
- Hyperglycaemia and diabetes mellitus

Education material for physician and health care professionals
Objective and Rationale: The key aim of educational activities for physicians and other HCPs is to give guidance, based on the SmPC, to ensure the safe and appropriate use of quetiapine in patients with bipolar depression to introduce physicians to the indication, the recommended dosing regimen, and the benefit/risk profile.
Propose Action: MAH will distribute education material for physician and healthcare professionals

VI.2.6 Planned post authorisation development plan

No studies planned.

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

Version	Date	Safety Concern	Comment
3.0	12 April 2016	In the RMP, missing information "Safety in patients on concomitant valproic acid" has been modified to important potential risk as "concomitant use of valproic acid".	As per RMS Day 120 Draft Assessment report for Quetiapine Accord (UK/H/3524/005/DC), the RMP has been updated. As per CMS Day 145 comments for Quetiapine Accord (UK/H/3524/005/DC), the RMP has been updated.

<table>
<tr>
<td>2.0</td>
<td>03 November 2015</td>
<td colspan="2">RMP has been updated with below safety concerns:</td>
<td rowspan="2">Additional Risk minimisation measures have been proposed for safety concerns “metabolic risk factors, extrapyramidal symptoms, somnolence, weight gain, lipid changes (increased cholesterol [including increased LDLs], increased triglycerides, and decreased HDLs), hyperglycaemia and diabetes mellitus and potential for off-label use and misdosing”.

As per Day 70 and Day 100 Preliminary assessment report for Quetiapine Accord (UK/H/3524/005/DC), the</td>
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<tr>
<td></td>
<td></td>
<td>Important identified risks (s)</td>
<td>• Hyperglycaemia and diabetes
• Hypothyroidism
• Increased blood pressure in paediatric population
• Agranulocytosis
• QT prolongation
• Metabolic risk factors
• Venous thromboembolism
• Pancreatitis</td>
</tr>
</table>

Version	Date	Safety Concern	Comment
		• Extrapyramidal symptoms • Tardive dyskinesia • Somnolence • Syncope and orthostatic hypotension • Seizure • Neutropenia • Weight gain • Lipid changes (increased cholesterol (including increased LDLs), increased triglycerides, and decreased HDLs) • Hyperprolactinaemia • Anaphylactic reaction • Jaundice, hepatitis and	RMP has been updated.

Version	Date	Safety Concern		Comment
			increased serum transaminase and gamma-glutamyl transpeptidase (GGT) • Stevens johnson syndrome • Neuroleptic malignant syndrome • Withdrawal (discontinuation) symptoms and neonatal withdrawal • Dysphagia • Intestinal obstruction • Hyponatraemia and syndrome of inappropriate antidiuretic hormone secretion (SIADH)	
		Important	• Safety in elderly	

			potential risks	patients • Cerebrovascular adverse effects in elderly patients • Cerebrovascular adverse effects in non-elderly patients • Ischaemic heart disease • Aggression/ agitation • Suicide and suicidality • Aspiration pneumonia • Potential for off-label use and misdosing • Torsade de pointes • Increased mortality in elderly demented patients • Abuse and misuse Accidental injury		

		Missing information	• Safety in pregnant or breastfeeding women • Safety in patients on concomitant cardiovascular medications • Safety in patients on concomitant valproic acid		•