VI: 2 ELEMENTS FOR A PUBLIC SUMMARY

Quetiapine is a type of medication known as an antipsychotic medicine. The medicine is available in two forms: SEROQUEL and SEROQUEL XR/XL (a slow-releasing form), hereafter SEROQUEL/SEROQUEL XR. SEROQUEL/SEROQUEL XR works by correcting imbalances of chemical substances which act on the brain and nervous system. SEROQUEL/SEROQUEL XR is used to treat schizophrenia, bipolar disorder, and Major Depressive Disorder.

Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of SEROQUEL/SEROQUEL XR has been established.

VI: 2.1 Overview of disease epidemiology

VI: 2.1.1 Schizophrenia

Schizophrenia is a serious mental health condition that causes disordered ideas, beliefs and experiences. Symptoms include hearing, seeing, or sensing things that are not real, having mistaken beliefs, and feeling unusually suspicious. The incidence of schizophrenia is variable across countries, but tends to be higher in more developed countries. In men, the highest risk of developing schizophrenia is between 18 and 25 years of age; women aged between 26 and 45 years, and between 55 to 64 years have a higher risk of developing schizophrenia. People who have other family members with schizophrenia have a higher risk of developing the condition, and schizophrenia tends to be more common in people with lower family incomes. If untreated, people with schizophrenia have a higher risk of death.

Schizophrenia may be treated with antipsychotics medicines, as well as non-drug treatments such as behavioural therapy and counselling.

VI: 2.1.2 Bipolar disorder

Bipolar disorder is a life-long illness that causes periods of depression (lows) and periods of mania (highs), affecting mood, energy, and ability to function. Bipolar I patients have intense mania, while Bipolar II patients have less severe mania (known as hypomania). All bipolar patients spend more time depressed than manic or hypomanic.

People aged around 20 years old have the highest risk of developing bipolar disorder; risk reduces with increasing age. Bipolar I occurs in men and women equally: Bipolar II is more common in women. The chances of developing bipolar disorder are unrelated to race or family income. If untreated, bipolar patients have a higher risk of other mental health and medical conditions, and a higher risk of death, especially suicide.

Bipolar patients may be treated with various medications or combinations of medications including antipsychotics, antidepressants, mood stabilisers such as lithium, anti-epileptic medicines and non-drug treatments such as behavioural therapy and counselling.

VI: 2.1.3 Major Depressive Disorder

Major depression is a medical illness that causes a continual feeling of sadness and loss of interest, usually requiring long-term treatment. The incidence of major depression is variable across European countries. People aged between 18 and 30 have the highest risk of developing major depression: it is also more common in women than in men, and in people with other long-term diseases such as Parkinson’s disease, chronic pain, stroke, heart disease, AIDS, lung diseases, thyroid diseases and cancer. Having other mental health problems such as anxiety or personality disorders, or abusing drugs or alcohol, may also increase the risk of developing major depression. If untreated, major depression can increase the risk of death.

Major depression may be treated with antidepressants (sometimes in combination with other medicines, including antipsychotics). Electric shock treatment is an option for patients who do not respond to standard drug treatments.

VI: 2.2 Summary of treatment benefits

SEROQUEL/SEROQUEL XR is a type of medication known as an antipsychotic medicine which works by correcting imbalances of chemical substances which act on the brain and nervous system. Because SEROQUEL/SEROQUEL XR only acts specifically with certain chemicals in the brain, patients taking SEROQUEL/SEROQUEL XR may experience a lower level of certain side effects, such as muscle spasms, restlessness, shaking or rigidity.

Over 28,000 adult patients have received SEROQUEL or SEROQUEL XR in clinical studies. SEROQUEL XR releases medicine more slowly than SEROQUEL.

There have been five clinical studies in schizophrenia which showed that SEROQUEL XR treatment significantly increased the time to a schizophrenic episode in clinically stable patients treated for up to 9 months. Data from clinical studies demonstrate that SEROQUEL is effective in the dose range of 150 to 750 mg daily (400 to 800 mg daily for SEROQUEL XR).

There have been eleven clinical studies of SEROQUEL and SEROQUEL XR in the treatment of bipolar disorder which showed that SEROQUEL and SEROQUEL XR are effective in the treatment of both depressive and manic episodes and that continued treatment, either alone or in combination with other mood stabilisers such as lithium or valproate, increased the time to an episode of depression or mania taking place. A study on long term treatment showed that benefits were maintained for up to one year. Data showed that a range of 300 to 800 mg daily was effective.

There have been eight clinical studies in major depression which showed that giving SEROQUEL XR at a dose of 150 to 300 mg daily was effective in patients who had not responded to initial treatment with standard antidepressants.

VI: 2.3 Unknowns relating to treatment benefits

Most clinical studies excluded seriously ill patients (heart, liver or kidney failure; uncontrolled diabetes), pregnant women and patients with recent suicide attempts. Reduced doses are recommended in patients with liver damage and standard doses in patients with kidney damage. Babies of women using SEROQUEL/SEROQUEL XR during pregnancy may experience withdrawal effects.

VI: 2.4 Summary of safety concerns

This section presents a summary of important identified risks, important potential risks and important missing information; these are defined as follows:

- An important identified risk is an important side effect that is known to be related to the medicine of interest.

- An important potential risk is an important side effect that is suspected to be related to the medicine of interest but a connection has not been confirmed. It is not known

whether the potential risks described in this summary are due to the use of SEROQUEL/SEROQUEL XR.

- Important missing information is information about the safety of a medicine that is not available when the medicine was approved for sale. This may be unknown information about the safety of the medicine for conditions for which it is not approved for use.

Inclusion of information relating to a potential risk should not be taken to imply that causal association with the use of SEROQUEL/SEROQUEL XR has been established.

For SEROQUEL/SEROQUEL XR, important identified risks, important potential risks and important missing information are provided in Table VI-4, Table VI-5, and Table VI-6, respectively.

Table VI-4 Important identified risks

Risk	What is known	Preventability
Abnormal muscle movements such as muscle spasms, restlessness, shaking, rigidity, muscle stiffness without pain.	Approximately 1 in 10 of all patients in SEROQUEL/SEROQUEL XR clinical studies experienced uncontrollable muscle movements resulting from drug treatment. Patients with bipolar disorder appeared to be more likely to experience these effects compared with patients with schizophrenia	Doctors and patients are made aware of the increased risk of abnormal muscle movements in the SEROQUEL/SEROQUEL XR product information. Medication adjustments may be necessary.
Uncontrollable movements, mainly of the face or tongue	1 in 500 of all patients in SEROQUEL/SEROQUEL XR clinical studies experienced uncontrollable movements of the face or tongue	Doctors and patients are made aware of uncontrollable movements, mainly of the face or tongue in the SEROQUEL/SEROQUEL XR product information. If these movements occur, lowering the dose or discontinuation of SEROQUEL/SEROQUEL XR should be considered. These movements may occur or worsen after treatment stops.

Table VI-4 Important identified risks

Risk	What is known	Preventability
Feeling sleepy	Approximately 42 in 100 of all patients in SEROQUEL/SEROQUEL XR clinical studies reported feeling sleepy after starting treatment with SEROQUEL/SEROQUEL XR.	Patients should be aware of the risk of feeling more sleepy when starting SEROQUEL/SEROQUEL XR treatment. The effect of feeling sleepy may be reduced by using a lower dose. The effects may also reduce with time, if SEROQUEL/SEROQUEL XR is continued. Patients should not drive or use any tools or machines until they know how the tablets affect them.
Feeling faint and low blood pressure	Approximately 3 in 100 of all patients in SEROQUEL/SEROQUEL XR clinical studies reported feeling faint, or had low blood pressure after starting treatment with SEROQUEL/SEROQUEL XR.	The effects of feeling faint and low blood pressure were more common shortly after starting SEROQUEL/SEROQUEL XR treatment. Slowly increasing the dose of SEROQUEL/SEROQUEL XR over time may reduce the risk of these events. Patients with heart problems or low blood pressure should be careful until they know how the tablets affect them.
Fits (seizures)	Approximately 1 in 300 of all patients in SEROQUEL/SEROQUEL XR clinical studies experienced a fit (seizure) after starting treatment with SEROQUEL/SEROQUEL XR.	No specific risk prevention measures have been identified
Reductions in white blood cell counts	Approximately 1 in 250 patients in SEROQUEL/SEROQUELXR clinical studies had reduced white blood cell counts after starting treatment with SEROQUEL/ SEROQUELXR.	Patients who already have low white blood cell counts, or patients who have previously had reductions in white blood cells caused by other medications may be at a higher risk. Reductions in white blood cell counts have resolved after SEROQUEL/SEROQUEL XR therapy has been discontinued.
Severe reductions in a type of white blood cell called neutrophils (agranulocytosis)	Severe reductions in a type of white blood cell called neutrophils have only been seen in 1 patient in the SEROQUEL/ SEROQUELXR clinical studies, and there have been rare reports of this effect with use of the marketed product.	No specific risk prevention measures have been identified. SEROQUEL/SEROQUEL XR should be discontinued in patients with a neutrophil count of less than 100 cells per microlitre and patients should be observed for signs and symptoms of infection until their neutrophil count is above 150 cells per microlitre

Table VI-4 Important identified risks

Risk	What is known	Preventability
Weight gain	Approximately 1 in 5 of all patients in SEROQUEL/ SEROQUELXR clinical studies had weight gain of 7% or more compared with baseline.	A healthy diet and exercise are recommended for patients at risk for weight gain.
Changes in cholesterol levels	The following changes in cholesterol levels were seen in patients in SEROQUEL/ SEROQUEL XR clinical studies: increases in total cholesterol (approximately 1 in 10 patients), triglycerides (approximately 1 in 5 patients), and LDL (bad) cholesterol (approximately 7 in 100 patients), with decreases in HDL (good) cholesterol (approximately 15 in 100 patients).	A healthy diet and exercise are recommended for patients at risk for increased cholesterol. For some patients, a cholesterol lowering medication may be required.
High blood sugar levels and diabetes	Approximately 3 in 100 patients in SEROQUEL SEROQUELXR / clinical studies developed high blood sugar levels after starting treatment with SEROQUEL/ SEROQUELXR.	Weight reduction, blood pressure control, cholesterol control, diet, and exercise are recommended in patients at risk for development of diabetes.
Metabolic syndrome risk factors (metabolic syndrome describes a combination factors that, when occurring together, increase the risk of developing heart disease and diabetes)	Approximately 1 in 10 patients in SEROQUEL/ SEROQUELXR clinical studies shifted their risk score for metabolic syndrome from less than 3 (low risk) to 3 or more (high risk) after starting treatment with SEROQUEL/SEROQUELXR.	Weight reduction, blood pressure control, cholesterol control, diet, and exercise are recommended in patients at risk for development of metabolic syndrome.
Low blood sodium levels and harmful effects on a hormone that controls urine volume (anti-diuretic hormone)	After starting treatment with SEROQUEL/ SEROQUELXR, approximately 1 in 2,000 patients in SEROQUEL/ SEROQUELXR clinical studies developed low blood sodium and harmful effects on a hormone that controls urine volume.	No specific risk prevention measures have been identified.
Underactive thyroid (hypothyroidism)	Approximately 1 in 150 patients in SEROQUEL/ SEROQUEL XR clinical studies developed an underactive thyroid after starting treatment with SEROQUEL/ SEROQUEL XR.	Changes in the amount of thyroid hormones in your blood are seen only when a blood test is taken. These changes occur most often in the first 6 weeks of treatment, with no further change during long-term treatment. Most thyroid changes resolve (two-thirds of all cases) when SEROQUEL/SEROQUEL XR treatment is discontinued.

Table VI-4 Important identified risks

Risk	What is known	Preventability
Increased levels of a hormone which affects breast size and the production of breast milk	Approximately 1 in 20 patients, both men and women, in SEROQUEL/SEROQUEL XR clinical studies experienced increased levels of a hormone which affects breast size and the production of breast milk (prolactin). In some cases, this led to swelling of breasts and unexpected production of breast milk after starting treatment with SEROQUEL/SEROQUEL XR.	Doctors and patients are made aware of the effects of increased levels of prolactin, a hormone which affects breast size and the production of breast milk, in the SEROQUEL/SEROQUEL XR product information. Changes in the amount of hormones in your blood are seen only when a blood test is taken.
Severe allergic (anaphylactic) reaction	No patients in the SEROQUEL/SEROQUEL XR clinical studies experienced severe allergic reactions (anaphylaxis). However, there have been very rare reports of this event with use of the marketed product.	No specific risk reduction measures have been identified
Liver effects: Hepatitis with or without Jaundice	**Hepatitis** Approximately 1 in 2,500 patients in SEROQUEL/SEROQUEL XR clinical studies developed hepatitis after starting treatment with SEROQUEL/SEROQUEL XR. **Jaundice** Approximately 6 in 10,000 patients in SEROQUEL/SEROQUEL XR clinical studies developed jaundice after starting treatment with SEROQUEL/SEROQUEL XR. Based on post-marketing. There is a risk that persistent changes in liver function tests may lead to permanent liver damage.	SEROQUEL/SEROQUEL XR should be used with caution in patients with known liver problems, especially at the start of treatment. Jaundice may cause yellowing of the skin and eyes.
Serious skin reactions (Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Erythema Multiforme)	No patients in the SEROQUEL/SEROQUEL XR clinical studies experienced serious skin reactions. However, there have been very rare reports of this effect with use of the marketed product.	No specific risk reduction measures have been identified
A combination of high temperature (fever), sweating, stiff muscles, feeling very drowsy or faint, large increase in blood pressure or heartbeat (a disorder called Neuroleptic Malignant Syndrome).	Approximately 1 in 10,000 patients in the SEROQUEL/SEROQUEL XR clinical studies developed neuroleptic malignant syndrome after starting treatment with SEROQUEL/SEROQUEL XR	If the combination of symptoms known as Neuroleptic Malignant Syndrome occurs, SEROQUEL/SEROQUEL XR should be discontinued and appropriate medical treatment given.

Table VI-4 Important identified risks

Risk	What is known	Preventability
Withdrawal (discontinuation) symptoms including withdrawal effects in babies whose mothers have taken SEROQUEL/SEROQUEL XR during pregnancy	In the short-term SEROQUEL/SEROQUEL XR studies in major depression, approximately 1in 6 patients treated with SEROQUEL/SEROQUEL XR developed withdrawal effects such as not being able to sleep, feeling or being sick, headache, diarrhoea, dizziness and irritability. A small number of women in the SEROQUEL/SEROQUEL XR clinical studies became pregnant whilst taking SEROQUEL/SEROQUEL XR. Withdrawal symptoms were occasionally seen in the babies of these women.	SEROQUEL/SEROQUEL XR treatment should be gradually reduced over a period of at least one to two weeks before treatment is stopped. Mothers who use SEROQUEL/SEROQUEL XR during the last 3 months of their pregnancy may have newborn babies who experience withdrawal effects (shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding). These babies should be monitored carefully.
Swallowing problems	Approximately 1 in 200 patients in the SEROQUEL/SEROQUEL XR clinical studies had difficulty swallowing after starting treatment with SEROQUEL/SEROQUEL XR	SEROQUEL/SEROQUEL XR should be used carefully in patients who are at risk for aspiration pneumonia, resulting from swallowing problems.
Inflammation of the pancreas (pancreatitis)	Approximately 1 in 2,500 patients in the SEROQUEL/SEROQUEL XR clinical studies developed inflammation of the pancreas after starting treatment with SEROQUEL/SEROQUEL XR	No specific risk prevention measures have been identified.
Blockage of the bowel	Approximately 1 in 1,000 patients in the SEROQUEL/SEROQUEL XR clinical studies experienced blockage of the bowel after starting treatment with SEROQUEL/SEROQUEL XR	Constipation is a risk factor for blockage of the bowel. The risk of blockage of the bowel could be minimized if severe constipation is detected and treated.

Table VI-4 Important identified risks

Risk	What is known	Preventability
Changes in electrical activity of the heart	Approximately 1 in 1,000 patients in the SEROQUEL/SEROQUEL XR clinical studies had changes in electrical activity of the heart after starting treatment with SEROQUEL/SEROQUEL XR.	SEROQUEL/SEROQUEL XR should be used with care in patients with heart disease or a family history of changes in the electrical activity of the heart. Caution should also be taken when SEROQUEL/SEROQUEL XR is given at the same time as other medicines known to affect the electrical activity of the heart, including other antipsychotic medicines. This is especially true for patients with heart electrical activity abnormalities or a family history of such abnormalities, elderly patients, patients with low levels of sodium or magnesium in the blood, and patients with heart failure or an increased heart size. Patients who have taken an overdose of SEROQUEL/SEROQUEL XR should be observed for any changes in the electrical activity of the heart.
Blood clots in the veins (deep vein thrombosis)	Approximately 8 in 10,000 patients in the SEROQUEL/SEROQUEL XR clinical studies developed blood clots in the veins (especially in the legs) as a result of SEROQUEL/SEROQUEL XR treatment	Patients with factors which may increase the risk of developing a blood clot in the veins (eg, those who have been hospitalized, have a major medical condition such as cancer or heart failure, patients who have had recent major surgery or injury) should be aware of the risk of blood clots. Blood clots can be treated if detected at an early stage.
Increased blood pressure in children taking SEROQUEL/SEROQUEL XR	Studies in children with SEROQUEL/SEROQUEL XR have shown that some patients develop high blood pressure after starting treatment with SEROQUEL/SEROQUEL XR. These effects are not seen in adult patients.	In the European Union, SEROQUEL/SEROQUEL XR is not approved for children and adolescents (10 to 17 years).

XR extended release.

Table VI-5 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Stroke	In clinical studies, stroke was seen in approximately 1 in 50 elderly patients (more than 65-years-old) after starting treatment with SEROQUEL/SEROQUEL XR. In non-elderly patients, the frequency of patients experiencing stroke was approximately 1 in 1,000.
Reduced blood supply to the heart (ischemic heart disease)	Reduced blood supply to the heart (ischemic heart disease) is considered an effect which is observed with other antipsychotic medicines of the same type as SEROQUEL/SEROQUEL XR. In the SEROQUEL/SEROQUEL XR clinical studies, approximately 1 in 375 patients had ischemic heart disease.
Increased risk of death in elderly patients with dementia	An increased risk of death in elderly patients with dementia is considered an effect which is observed with other antipsychotic medicines of the same type as SEROQUEL/SEROQUEL XR. All deaths in elderly patients with dementia have been reviewed; it has been concluded that a higher number of these patients died on SEROQUEL/SEROQUEL XR treatment compared with another antipsychotic medicine (haloperidol); however, the data do not establish a relationship between SEROQUEL/SEROQUEL XR treatment and death in elderly patients with dementia. SEROQUEL/SEROQUEL XR does not have approval to be given to elderly patients as a treatment for dementia-related mental health problems.
Aggression/agitation	Aggression/agitation is considered an effect which is observed with other antipsychotic medicines of the same type as SEROQUEL/SEROQUEL XR. In the SEROQUEL/SEROQUEL XR clinical studies, approximately 7 in 100 patients had an event of aggression and/or agitation.
Abuse and misuse	Abuse/misuse is considered an effect which is observed with other antipsychotic medicines of the same type as SEROQUEL/SEROQUEL XR. In the SEROQUEL/SEROQUEL XR clinical studies, approximately 7 in 10,000 patients had an event of abuse or misuse.
Suicide and suicidality	Patients with schizophrenia, bipolar disorder and major depression have a higher risk for suicide than patients who do not have these diseases. Approximately 1 in 100 patients in the SEROQUEL/SEROQUEL XR clinical studies had an event associated with suicide or suicidal behaviour.
Accidental injury	Accidental injury is an event that may be indirectly related to other, more clearly established drug effects, such as feeling sleepy or dizziness. In the SEROQUEL/SEROQUEL XR clinical studies, 1 in 50 patients had an event associated with an accidental injury.
Serious lung infection caused by food, drink or saliva getting into the airway (aspiration pneumonia)	In the SEROQUEL/SEROQUEL XR clinical studies approximately 1 in 200 had a lung infection associated with food, drink or saliva getting into the airway. Patients taking SEROQUEL/SEROQUEL XR may be at a higher risk of developing this condition because of their condition, other mental health problems, or other medications they are taking.
Potential for off-label use and misdosing	Antipsychotic medicines like SEROQUEL/SEROQUEL XR are often used in situations that have not been tested in clinical studies, and therefore to treat patients or diseases, or to use doses, that they are not specifically approved for. Although AstraZeneca does not support the use of its products for off-label or unapproved uses, there is a potential that SEROQUEL/SEROQUEL XR will be used in such situations.

Table VI-5 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Use in elderly patients	Small studies of SEROQUEL/SEROQUEL XR in elderly men and women with mental health problems have shown that the medicine is not removed from the body as fast as it is in younger patients. Therefore, doses may need to be increased more slowly, and lower doses may be effective in the elderly population, depending on the individual patient. The effectiveness and safety of SEROQUEL/SEROQUEL XR has not been studied in patients over 65 years of age with depressive episodes related to bipolar disorder.

Table VI-6 Important missing information

Risk	What is known
Use in pregnant or breast feeding women	Women were not allowed to take part in the SEROQUEL/SEROQUEL XR clinical studies if they were pregnant. However, some women became pregnant during clinical studies. Following pregnancies in which SEROQUEL/SEROQUEL XR was used, some babies displayed withdrawal symptoms. If you are pregnant or breast feeding, think you may be pregnant or planning to have a baby ask your doctor for advice before taking Seroquel XR. You should not take Seroquel XR during pregnancy unless this has been discussed with your doctor. Seroquel XR should not be taken if you are breast-feeding.
Use in patients taking medications for heart conditions	The effects of SEROQUEL/SEROQUEL XR when given at the same time as other medicines which affect the heart have not been formally studied. Because some patients in the SEROQUEL/SEROQUEL XR clinical studies had changes in electrical activity of the heart after starting treatment, SEROQUEL/SEROQUEL XR should be used with care in patients with heart disease or a family history of changes in the electrical activity of the heart. Caution should also be taken when SEROQUEL/SEROQUEL XR is given at the same time as other commonly used medicines taken for heart conditions, or other medicines known to affect the electrical activity of the heart, including other antipsychotic medicines. This is especially true for patients with heart electrical activity abnormalities or a family history of such abnormalities, elderly patients, patients with low levels of sodium or magnesium in the blood and patients with heart failure or an increased heart size.
Use in patients taking the anti-epileptic medicine valproic acid (valproate)	A small study of SEROQUEL and valproate taken at the same time found that the combination of the two products was generally safe and well tolerated.

VI: 2.5 Summary of additional 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 reducing them. An easier-to-read summary of

this information is provided in the form of the patient information leaflet (PIL). The information in these documents is known as routine risk minimisation (reduction) measures.

SEROQUEL/SEROQUEL XR has special conditions and restrictions for its safe and effective use (additional risk reduction measures). The way in which these special conditions are put into practice across the European Union may be different for different countries.

These additional risk reduction measures are for the risks described in Table VI-7 to Table VI-12.

Table VI-7 Abnormal muscle movements

Risk minimisation measure(s): Healthcare Professional education
Objective and rationale
To reduce the known risk that SEROQUEL/SEROQUEL XR can cause abnormal muscle movement, clear guidelines are needed for physicians to enable early detection of any abnormal muscle movement and to ensure the appropriate actions are taken to treat any changes that do occur.
Main additional risk minimisation measures
• Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on abnormal muscle movement with a reference to the local prescribing information for details • Educational programmes on the risks and benefits of SEROQUEL/SEROQUEL XR, delivered by company sales representatives

Table VI-8 Sleepiness

Risk minimisation measure(s): Healthcare Professional education
Objective and rationale
To reduce the known risk that SEROQUEL/SEROQUEL XR can cause sleepiness, clear guidelines are needed for physicians to enable early detection of any problems with patients' sleep patterns and to ensure the appropriate actions are taken to treat any changes that do occur
Main additional risk minimisation measures
• Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on sleep patterns with a reference to the local prescribing information for details • Educational programmes on the risks and benefits of SEROQUEL/SEROQUEL XR, delivered by company sales representatives

Table VI-9 Weight gain

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To reduce the known risk that SEROQUEL/SEROQUEL XR can cause weight gain, clear guidelines are needed for physicians to enable early detection of any problems with patients' weight and to ensure the appropriate actions are taken to treat any changes that do occur

Main additional risk minimisation measures

- Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on patients' weight
- Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including weight gain

Table VI-10 High blood sugar levels and diabetes

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To reduce the known risk that SEROQUEL/SEROQUEL XR can cause increases in blood sugar and diabetes, clear guidelines are needed for physicians to enable early detection of any problems with patients' blood sugar levels and to ensure the appropriate actions are taken to treat any changes that do occur

Main additional risk minimisation measures

- Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on patients' blood sugar levels
- Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including high blood sugar levels and diabetes

Table VI-11 Changes in blood cholesterol levels

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To reduce the known risk that SEROQUEL/SEROQUEL XR can cause changes in blood cholesterol levels, clear guidelines are needed for physicians to enable early detection of any problems with patients' cholesterol levels and to ensure the appropriate actions are taken to treat any changes that do occur

Main additional risk minimisation measures

Educational activities and materials

- Provide additional printed information (eg a laminated card, brochure, or similar document) to remind physicians of the risks of SEROQUEL/SEROQUEL XR treatment on patients' cholesterol levels
- Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including cholesterol levels

Table VI-12 Metabolic syndrome risk factors

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To reduce the known risk that SEROQUEL/SEROQUEL XR can cause increase the risk factor for metabolic syndrome (a combination of factors that, when occurring together, increase the risk of developing heart disease and diabetes), clear guidelines are needed for physicians to enable early detection of any problems with patients' cholesterol levels and to ensure the appropriate actions are taken to treat any changes that do occur.

Main additional risk minimisation measures

Educational activities and materials

- Provide additional printed information (eg, a laminated card, brochure, or similar document) to remind physicians of the risks that SEROQUEL/SEROQUEL XR treatment may increase a patient's risk of developing metabolic syndrome
- Educational programme describing the effects of SEROQUEL/SEROQUEL XR treatment on the metabolism, including the possibility of an increased risk factor for metabolic syndrome

Table VI-13 Potential for off-label use and misdosing

Risk minimisation measure(s): Healthcare Professional education

Objective and rationale

To provide clear guidance on the safe and appropriate use of SEROQUEL/SEROQUEL XR.

Main additional risk minimisation measures

Educational activities and materials

- Core guidance document ensuring consistent capture of indication from spontaneous postmarking reports
- The key aim of educational activities for health care professionals is to give guidance, based on the product information, to ensure the safe and correct use of SEROQUEL/SEROQUEL XR. To ensure such use in patients with bipolar depression, AstraZeneca developed informational material to introduce physicians to the recommended dosing schedule.

VI: 2.6 Planned post authorisation development plan

Table VI-14 List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study D144AC00004 Study of real-life clinical use of SEROQUEL XR in England	To examine the safety and use of SEROQUEL XR in England, with abnormal muscle movements and sleepiness being of special interest in the approved bipolar depression indication To quantify the incidence of frequently and rarely reported events	Safe use of SEROQUEL XR in real-life clinical practice (especially the effect on abnormal muscle movements and sleepiness)	Nested case control ongoing	FVAR received Nested case control studies: 4Q2014
Study D1444C00006 Study of real-life clinical use of SEROQUEL XR in the UK	To compare new users of SEROQUEL XR in the UK with new users of other antipsychotic drugs and examine the safety of SEROQUEL XR	Safe use of SEROQUEL XR in real-life clinical practice	Completed	Assessment report received
Study D1444C00011 Safety of SEROQUEL and SEROQUEL XR in a real-life hospital setting	To monitor the short-term (up to 12 weeks) use and safety of SEROQUEL/SEROQUEL XR in patients with schizophrenia or with manic episodes associated with bipolar disorder by psychiatrists under normal conditions of use	Safety comparison of SEROQUEL and SEROQUEL XR in real-life clinical practice	Completed	Assessment report received
Study D1443C00057 EU Drug Utilisation Study of SEROQUEL XR in severe depression	Real life clinical practice use of SEROQUEL XR for treatment of severe depression	Not applicable	Ongoing	Assessment report received CSR expected 4Q2014
Study D1443C00056 Study of real-life clinical use of SEROQUEL and SEROQUEL XR in Sweden	Real life clinical practice use of SEROQUEL and SEROQUEL XR Use of SEROQUEL XR for the treatment of severe depression, in comparison with other antidepressants	Safety of SEROQUEL and SEROQUEL XR in real-life clinical practice and potential for off-label use and misdosing	Ongoing	Part I - Pilot report: 13 Dec 2012 Part II DU - First report: 14 June 2013 Part II DU – Second report: 23 May 2014 Part III – Safety report (planned): 2015 or 2016 depending upon use/ exposure

Table VI-14 List of studies in post authorisation development plan

Study/activity (including study number)	Objectives	Safety concerns /efficacy issue addressed	Status	Planned date for submission of (interim and) final results
Study D1443L00091 Study of real-life clinical use in France	To study the patients using SEROQUEL XR in real-life practice in France To look at the health of patients schizophrenia or acute bipolar disorder and what other healthcare services they need for up to 1 year after receiving SEROQUEL XR	Safety of SEROQUEL XR in real-life clinical practice	Ongoing	Final report estimated to be available late 2015
Study D1443C00127 Assessment of educational materials	Effectiveness of metabolic syndrome education materials	Effectiveness of additional risk minimisation measures	Completed	FVAR received
Study D1443C00128 Electronic Medical Record study	Effectiveness of metabolic syndrome education materials	Effectiveness of additional risk minimisation measures	Completed	FVAR received

UK United Kingdom; XL/XR Extended release.

Studies which are a condition of the marketing authorisation

All of the studies listed in Table VI-14 are conditions of the marketing authorisations for SEROQUEL and/or SEROQUEL XR.

VI: 2.7 Summary of changes to the Risk Management Plan over time

Table VI-15 Summary of changes to the Risk Management Plan over time

RMP Version number	Date of authorisation of the RMP	Formulation	Summary of changes
13	**Pending**	SEROQUEL and SEROQUEL XR	The following identified or potential risks or information considered missing, were deleted per procedure number NL/H/0156/001-012/IB/110 final variation assessment report: dysarthria, rhabdomyolysis, serotonin syndrome, sudden death, myocarditis, cataract, risk in patients with hepatic impairment for all SEROQUEL formulations, us in patients with renal disease, use in patients with different ethnic or racial origin, treatment emergent mania in patients with bipolar depression and use in patients with longer exposure. The three risks that comprised Liver Disorder (Hepatitis, Jaundice and elevated liver enzymes have been combined into one risk, Hepatitis with or without jaundice. SEROQUEL/SEROQUEL XR clinical safety database was updated and clinical tables reflect the changes from version 26 to version 27. Experience of SEROQUEL marketed products information was updated. For the risks that contain post-marketing information, the numbers of patients experiencing adverse events was updated through 12 June 2014. PASS information has been updated to reflect the current status of these studies. Risk minimization activities have been updated. Changes to the SmPCs as a result of the harmonization process are reflected in this EU-RMP.
12	31Jan 2014	SEROQUEL and SEROQUEL XR	Blockage of bowel and withdrawal effects in babies have been added as identified risks. Risk tables have been provided in a new format. Experience of SEROQUEL marketed products information has been updated. Risk minimisation activities have been updated and Asian patients are no longer considered missing information.
11	13 Aug 2012	SEROQUEL and SEROQUEL XR	The following potential risks were changed to identified risks: severe reductions in a type of white blood cell called neutrophils, metabolic syndrome risk factors, muscle wasting, inflammation of the pancreas, changes in electrical activity of the heart, low blood sodium levels and harmful effects on a hormone that controls urine volume, and blood clots in the vein. Experience of SEROQUEL marketed products information was updated and risk minimisation activities were updated.

Table VI-15 Summary of changes to the Risk Management Plan over time

RMP Version number	Date of authorisation of the RMP	Formulation	Summary of changes
10	22 Sep 2012	SEROQUEL and SEROQUEL XR	Risk minimisation activities were updated and enhanced. The number of patients who have used SEROQUEL was updated. Information on the numbers of patients experiencing adverse events was updated, as were measures of monitoring the safety of patients using SEROQUEL, including the additional real-life clinical studies.
9	07 Dec 2009	SEROQUEL and SEROQUEL XR	Added new and newly characterised risks. Updated information from published literature. Added final results of cataract and sedation studies, and updated and enhanced risk minimisation activities.
8	19 Dec 2008	SEROQUEL and SEROQUEL XR	Bipolar depression was added to the uses of SEROQUEL (with update risk minimisation activities).
7	02 Sep 2008	SEROQUEL and SEROQUEL XR	Information was added on studies in generalised anxiety disorder and use in children.
6	21 Apr 2008	SEROQUEL XR	Severe depression added to the uses of SEROQUEL XR.
5	11 Apr 2008	SEROQUEL and SEROQUEL XR	Prevention of recurrence in bipolar disorder added to the uses of SEROQUEL.
4	15 Jan 2008	SEROQUEL and SEROQUEL XR	Update on information on bipolar depression and mania, and update on long term treatment in schizophrenia.
2	13 Jul 2007	SEROQUEL XR	Update on information on schizophrenia. Underactive thyroid was added as a potential risk and food-drug interactions were added as an identified risk (food-drug interactions were later deleted as risk, as this was no longer considered a risk). The name of the slow-releasing formulation was changed from SEROQUEL SR to SEROQUEL XR.
Unnumbered	18 Sep 2006	SEROQUEL SR	Schizophrenia was added to the uses of SEROQUEL SR.
Unnumbered	24 May 2006	SEROQUEL	Bipolar depression was added to the uses of SEROQUEL.

RMP Risk management plan. SR Sustained release; XR Extended release.