8.2 Part VI.2 Elements for a Public Summary

8.2.1 Part VI.2.1 Overview of disease epidemiology

Schizophrenia

By using precise methods in its diagnosis and a large, representative population, the incidence (a measure of the risk of developing some new condition within a specified period of time)rate of schizophrenia seems consistent across the world for the last half-century. [Häfner, 1997] Schizophrenia affects around 0.3–0.7% of people at some point in their life, [van, 2009] or 24 million people worldwide as of 2011 (about one of every 285). [WHO, 2011]

Schizophrenia occurs at similar rates worldwide, its prevalence (the proportion of a population found to have a condition) varies across the world, [Jablensky, 1992] within countries, [Kirkbride, 2006] and at the local and neighborhood level. [Kirkbride JB, 2007] It causes approximately 1% of worldwide disability-adjusted life years (DALYs). [Picchioni, 2007]

Bipolar Disorder

About 3% of people have bipolar disorder worldwide, a proportion consistent for both men and women and across racial and ethnic groups. The cause is not clearly understood, but both genetic and environmental risk factors are believed to play a role**.**

Bipolar disorder is the sixth leading cause of disability worldwide and has a lifetime prevalence of about 3% in the general population. [Boland, 2013], [Schmitt, 2014]. However, a reanalysis of data from the National Epidemiological Catchment Area survey in the United States suggested that 0.8% of the population experience a manic episode at least once (the diagnostic threshold for bipolar I) and a further 0.5% have a hypomanic episode (the diagnostic threshold for bipolar II or cyclothymia). The incidence of bipolar disorder is similar in men and women [Farren, 2012] as well as across different cultures and ethnic groups.

Depressive episodes

Depression is a major cause of morbidity worldwide [World Health Organization, 2001] Lifetime prevalence varies widely, from 3% in Japan to 17% in the US. In most countries the number of people who would suffer from depression during their lives falls within an 8–12% range. [Andrade, 2003], [Kessler, 2003]

In North America the probability of having a major depressive episode within any year-long period is 3–5% for males and 8–10% for females [Kessler RC, 2005], [Murphy, 2000].

8.2.2 Part VI.2.2 Summary of treatment benefits

Antipsychotic drugs are the gold standard in the treatment and relapse prevention of schizophrenia. A number of so-called “atypical antipsychotics” have been introduced since 1990 [Grohol, 2006], which have a lower risk of extrapyramidal symptoms than former antipsychotics. Quetiapine fumarate is one of these atypical antipsychotics.

The combination therapy of mood stabilizers like lithium with atypical antipsychotics is recommended as first-line treatment for severe bipolar mania. Quetiapine fumarate is an antipsychotic medicine which is used in patients with schizophrenia. Schizophrenia is a mental illness, in which patients suffer from hallucinations, disorganised thinking and speech, suspiciousness and delusions.

Quetiapine fumarate is also used for the prevention and treatment of bipolar disorder. Bipolar disorder is a mental illness in which patients have episodes of depression as well as manic episodes.

In clinical trials, Quetiapine fumarate has demonstrated efficacy against both positive and negative symptoms of schizophrenia. In comparative clinical trials, Quetiapine fumarate has been shown to be as effective as standard antipsychotic agents such as chlorpromazine and haloperidol. Quetiapine has an excellent risk/benefit profile and is a suitable first-line option for the treatment of schizophrenia [Cheer, 2004].

Recent clinical studies have shown that augmentation therapy with atypical antipsychotics like Quetiapine fumarate is effective in long-term maintenance treatment, and preliminary evidence is emerging that use of atypicals with mood stabilizers can help control the depressive phase of bipolar disorder [Bowden, 2005].

8.2.3 Part VI.2.3 Unknowns relating to treatment benefits

There is a lack of data to support use in children and adolescents below 18 years of age.

8.2.4 Part VI.2.4 Summary of safety concerns

The below listed safety concerns are applicable for both Quetiapine Prolonged-release tablets and Film-coated tablets.

Table 8-5 Important identified risks

Risk	What is known	Preventability
Inability to initiate movement or inability to remain motionless including involuntary asymmetrical movements of the muscles (Extrapyramidal symptoms [EPS]).	In a study of adult patients quetiapine was associated with an increased incidence of EPS compared to placebo in patients treated for schizophrenia (mental disorder often characterized by abnormal social behavior and failure to recognize what is real), bipolar mania (brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks) and bipolar depression (mental disorder characterized by periods of elevated mood and depression). Extrapyramidal symptoms include : Abnormal muscle movements. These include difficulty starting muscle movements, shaking, feeling restless or muscle stiffness without pain, uncontrollable movements, mainly of face or tongue.	A patient should immediately inform their doctor and dose reduction or discontinuation of quetiapine should be considered if he/she experiences any of the mentioned symptoms.
Feeling sleepy (Somnolence)	Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (feeling numb).	A patient should immediately inform their doctor if they experience severe sense of feeling sleepy as this may increase the risk of accidental

Risk	What is known	Preventability
	In clinical trials for treatment of patients with bipolar depression and major depressive disorder, onset of somnolence was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity.	injury (fall) in older people. A patient with major depressive episodes in MDD 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. As this medicine makes one sleepy, patient should not drive or use any tools or machines until he/she know how the tablets affect.
Weight gain	Weight gain has been reported very common in patients who have been treated with quetiapine.	Weight should be monitored and managed as clinically appropriate as in accordance with utilized antipsychotic guidelines. A patient and their doctor should check your weight regularly.
Changes of fat in the blood (Lipid changes)	While on Quetiapine, patients might experience elevations in types of fats in the blood, i.e. serum triglyceride levels and total cholesterol.	The triglyceride levels and the total cholesterol level should be monitored regularly, while under treatment with Quetiapine.
High blood sugar and chronic condition associated with abnormally high levels of sugar in the blood (Hyperglycaemia and diabetes diabetes mellitus)	Hyperglycaemia and/ or development or exacerbation of diabetes occasionally associated with ketoacidosis (potentially life-threatening complication in patients with diabetes) or coma (state of deep unconsciousness) has been reported rarely, including some fatal cases. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Signs and symptoms of hyperglycemia: Polydipsia (abnormally great thirst), polyuria (abnormally large volumes of dilute urine), polyphagia (excessive eating or appetite) and weakness.	Appropriate clinical monitoring is advisable in accordance with utilized antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycemiaPatients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.
Metabolic risk factors	Given the possible changes in	This requires appropriate

Risk	What is known	Preventability
	weight, blood glucose and lipids, patients could experience worsening of their metabolic risk factors: i.e. increase in fat around the abdomen, decrease in “good cholesterol” (HDL-C), increase in a type of fat in the blood called triglycerides, high blood pressure, increase in blood sugar.	medical treatment.

Table 8-6 Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Side effects associated with poor blood circulation in the brain in older people (Cerebrovascular adverse events in elderly)	Common side effects associated with cerebrovascular disease (conditions caused by problems that affect the blood supply to the brain) include: blurred vision, disturbance in speech and language and fits (seizures). Patients should tell their doctor if they have had a stroke previously, especially if they are older and also if they are an older person with dementia (loss of brain function). If they are older, 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 older people with dementia.
Side effects associated with poor circulation in the brain in non-older patients (Cerebrovascular adverse events in non-elderly patients)	Side effects associated with cerebrovascular disease (stroke) include: blurred vision, disturbance in speech and language and fits (seizures).
Very fast heartbeat caused by a malfunction in one of the heart's chamber (ventricles) associated with a heart rhythm disorder (Torsade de Pointes)	In post-marketing, QT prolongation (heart rhythm disorder) was reported uncommon side effect with quetiapine at the therapeutic doses and in overdose. As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with heart and/or blood vessels disease or family history of heart problems such as heart failure or irregular heartbeat, especially an abnormality known as “prolonged QT-interval”. A patient should talk to their doctor if he/she is taking any of the medicines that have an impact on the way the heart beats, for example, drugs that can cause an imbalance in electrolytes (low levels of potassium or magnesium) such as diuretics (a drug that increases the production of urine) or certain antibiotics (medicines used to treat bacterial infections).
Disease characterized by reduced blood supply to the heart (Ischemic heart disease)	Patients should talk to their doctor if they have or have had diseases of the heart and/or blood vessels (or a family history of heart problems) and if they have poor circulation in the heart

Risk	What is known (Including reason why it is considered a potential risk)
Use against the intended use and wrong dosing (Potential for off-label use and misdosing)	A patient should always take this medicine as prescribed by their doctor. Check with your doctor or pharmacist if not sure about the recommended dose. Quetiapine prolonged release should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.
Abuse and misuse	Currently available data do not support the need for risk minimization.

Table 8-7 Missing information

Risk	What is known (Including reason why it is considered a potential risk)
Use in pregnant and breast-feeding women	There have been published reports of quetiapine excretion into human breast milk; however the degree of excretion was not consistent. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine. If a patient is pregnant or thinks she may be pregnant or is planning to have a baby, the doctor or pharmacist should be asked for advice before taking this medicine. Quetiapine should not be taken if a patient is pregnant unless the doctor has told her to do.
Use in patients who are on medication for heart and/or vessel disorders (Use in patients on concomitant cardiovascular medication	No data on the safety in patients on concomitant cardiovascular medication is available.
Use in patients on concomitant valproic acid (a drug used for treatment of epilepsy or other illnesses)	A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia (a reduction in the number of white cells in the blood) and neutropenia (abnormally few neutrophils (neutrophilic white blood cell) in the blood) in the combination group versus the monotherapy groups. Medicines which act on the central nervous system can influence or be influenced by quetiapine. A patient should inform their doctor or pharmacist if he/she is taking, has recently taken or might take any other medicines.

8.2.5 Part VI.2.5 Summary of additional risk minimization measures by safety concern

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

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex 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:

Risk minimization measure(s)
Summary description of main additional risk minimization measures:
Inability to initiate movement or inability to remain motionless including involuntary asymmetrical movements of the muscles (Extrapyramidal symptoms
Objective and rationale: HCPs to understand what quetiapine is used for and be aware of the risk of extrapyramidal symptoms including tardive dyskinesia and how this should be mitigated and managed.
Proposed action:
The additional risk minimisation activity for quetiapine film-coated tablets and prolonged-release tablets, beyond the safety recommendations in the SPC, is an Educational material on the benefit : risk for physicians (i.e. treatment path guidance). It consists of a Physician leaflet together with the Summary of Product Characteristics to be provided to prescribing physicians including advice on: - instructions to patients - symptoms of extrapyramidal symptoms including tardive dyskinesia - dosing of the products - monitoring of patients during therapy - neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy. The educational material is provided in [Annex 11].

Risk minimization measure(s)
Summary description of main additional risk minimization measures:
Feeling sleepy (somnolence)
Objective and rationale: HCPs to understand what quetiapine is used for and be aware of the risk of somnolence and how this should be mitigated and managed.
Proposed action:
The additional risk minimisation activity for quetiapine film-coated tablets and prolonged-release tablets, beyond the safety recommendations in the SPC, is an Educational material on the benefit : risk for physicians (i.e. treatment path guidance).

Risk minimization measure(s)
It consists of a Physician leaflet together with the Summary of Product Characteristics to be provided to prescribing physicians including advice on: - physician's instructions to patients including caution about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating machinery in case of somnolence - details on relation between quetiapine therapy and somnolence. The educational material is provided in [Annex 11].

Risk minimization measure(s)
Summary description of main additional risk minimization measures:
Weight gain
Objective and rationale: HCPs to understand what quetiapine is used for and be aware of the risk of weight gain and how this should be mitigated and managed.
Proposed action:
The additional risk minimisation activity for quetiapine film-coated tablets and prolonged-release tablets, beyond the safety recommendations in the SPC, is an Educational material on metabolic parameters for physicians. It consists of a Physician leaflet together with the Summary of Product Characteristics to be provided to prescribing physicians including advice on: - physician's instructions to patients - details on early identification of modifiable risk factors, monitoring for further development of metabolic adverse effects and management of metabolic adverse effects. The educational material is provided in [Annex 11].

Risk minimization measure(s)
Summary description of main additional risk minimization measures:
Changes of fat in the blood (lipid changes)
Objective and rationale: HCPs to understand what quetiapine is used for and be aware of the risk of lipid changes and how this should be mitigated and managed.
Proposed action:
The additional risk minimisation activity for quetiapine film-coated tablets and prolonged-release tablets, beyond the safety recommendations in the SPC, is an Educational material on metabolic parameters for physicians. It consists of a Physician leaflet together with the Summary of Product Characteristics to be provided to prescribing physicians including advice on: - physician's instructions to patients - details on early identification of modifiable risk factors, monitoring for further development of metabolic adverse effects and management of metabolic adverse effects.

Risk minimization measure(s)
The educational material is provided in [Annex 11].

Risk minimization measure(s)
Summary description of main additional risk minimization measures:
High blood sugar and diabetes (hyperglycemia and diabetes mellitus)
Objective and rationale: HCPs to understand what quetiapine is used for and be aware of the risk of hyperglycemia and diabetes mellitus and how this should be mitigated and managed.
Proposed action:
The additional risk minimisation activity for quetiapine film-coated tablets and prolonged-release tablets, beyond the safety recommendations in the SPC, is an Educational material on metabolic parameters for physicians. It consists of a Physician leaflet together with the Summary of Product Characteristics to be provided to prescribing physicians including advice on: - physician's instructions to patients - details on early identification of modifiable risk factors, monitoring for further development of metabolic adverse effects and management of metabolic adverse effects. The educational material is provided in [Annex 11].

Risk minimization measure(s)
Summary description of main additional risk minimization measures:
Metabolic risk factors
Objective and rationale: HCPs to understand what quetiapine is used for and be aware of the risk of metabolic risk factors and how this should be mitigated and managed.
Proposed action:
The additional risk minimisation activity for quetiapine film-coated tablets and prolonged-release tablets, beyond the safety recommendations in the SPC, is an Educational material on metabolic parameters for physicians. It consists of a Physician leaflet together with the Summary of Product Characteristics to be provided to prescribing physicians including advice on: - physician's instructions to patients - details on early identification of modifiable risk factors, monitoring for further development of metabolic adverse effects and management of metabolic adverse effects. The educational material is provided in [Annex 11].

Risk minimization measure(s)
Summary description of main additional risk minimization measures:
Use against the intended use and wrong dosing (off-label use and misdosing)

Risk minimization measure(s)
Objective and rationale: HCPs to understand what quetiapine is used for and be aware of the risk of off-label use and misdosing and how this should be mitigated and managed.
Proposed action:
The additional risk minimisation activity for quetiapine film-coated tablets and prolonged-release tablets, beyond the safety recommendations in the SPC, is an Educational material for physicians with indication-specific educational pieces and activities, guidance document. It consists of a Physician leaflet together with the Summary of Product Characteristics to be provided to prescribing physicians including advice on: - physician's instructions to patients - known facts on off-label use of atypical antipsychotics such as quetiapine - off-label use of quetiapine should be discouraged - correct dosing / use of quetiapine. The educational material is provided in [Annex 11].

8.2.6 Part VI.2.6 Planned post authorization development plan

None

8.2.7 Part VI.2.7 Summary of changes to the Risk Management Plan over time

Major Changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
2.0	18 Dec 2014	- **Inclusion** of “Metabolic risk factors”, “Venous thromboembolism” and “Intestinal obstruction” **as important identified risks.** - **Inclusion** of “Ischemic heart disease”, “Aspiration pneumonia” **as important potential risks.** **- Inclusion** of “Safety in patients on concomitant cardiovascular medication” and “Safety in patients on concomitant valproic acid” **as missing information.** - **Upgrade** of “QT prolongation and Torsade de Pointes”, “Syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatraemia”, “pancreatitis”, “rhabdomyolysis” and “suicide” from important potential risk **to important identified risk.** “Suicide” was furthermore extended to “Suicide, suicidality and suicidal ideation” and “agranulocytosis” removed from important potential risk and added to the present important identified risk “Neutropenia”: now “Neutropenia including agranulocytosis. **Rewordings** of present risks: - “Increased cholesterol, increased triglycerides” changed to “Lipid changes” - “Elevations in serum prolactin” changed to “Hyperprolactinaemia” - “Withdrawal (discontinuation) symptoms” changed to “Withdrawal symptoms (including neonates)” - “Dysphagia in patients with bipolar depression (in the bipolar depression patient group)” changed to “Dysphagia” - “Cerebrovascular adverse events in the elderly” and “Cerebrovascular adverse events in non-elderly patients” merged to “Cerebrovascular adverse events” - “Potential for off-label use including off label pediatric use” changed to “Off-label use and misdosing” - “Use in breast-feeding women” changed to	Following the PVAR/CMS comments received on 26 Aug 2014 for Quetiapine Fumarate 200, 300, 400 mg Prolonged release tablet in NL/H/2140/001-002-003/II/006 the mentioned changes were made:

Version	Date	Safety Concerns	Comment
		"Safety in breast-feeding women"	
		- Inclusion of "Effect on human fertility" **as missing information.** **- Inclusion** of "Cardiomyopathy" **as important potential risk** ("Myocarditis and cardiomyopathy") **- Inclusion** of "Interaction with hepatic enzyme inducers" **as important identifies risk.** **- Upgrade** of "Use in pregnant women" **from missing information to important potential risk** ("Safety in pregnant women") - **Rewording** of "EPS including TD across all indications" to "Extrapyramidal (EPS) including tardive dyskinesia (TD)"	Additional changes independent from the mentioned PVAR/CMS comments
		Extrapyramidal symptoms, somnolence Weight gain, lipid changes, hyperglycemia and DM, metabolic risk factors Potential off-label use and misdosing	Educational program on benefit : risk for physicians (i.e. treatment path guidance) included Educational program on metabolic parameters for physicians included Educational program for physicians: Indication-specific educational pieces and activities, guidance document included
		N/A	The RMP was - updated to the currently valid EU-RMP template for generics, - Part II Module SV – Post-authorisation experience was added, - first approval and launch data of the film-coated and prolonged release tablets added in Part I: Product(s) overview and the marketing status of both formulations in Annex 3: Worldwide marketing status by country,
2.1	27 Mar 2015		Following the RMS Preliminary Variation Assessment Report for Quetiapine Sandoz retard 200/300/400 mg, prolonged release tablet Quetiapine fumarate in

Version	Date	Safety Concerns	Comment
		Dysarthria	NL/H/2140/001-003/II/006 the following changes were made: Added as important identified risk
		Suicide and suicidality	Deleted as important identified risk and included as an important potential risk, “suicidal ideation” deleted
		Use in pregnant and breast-feeding women	“Safety in pregnant women” deleted as important potential risk and “Safety in breastfeeding women” as missing information and added as combined missing information “Use in pregnant and breast-feeding women”
		Use of Quetiapine hemifumarate prolonged release tablets in patients with hepatic impairment Use of Quetiapine hemifumarate prolonged release tablets in elderly patients	Added as important potential risks
		Treatment-emergent mania patients with bipolar depression	Change to this important potential risk from “Treatment-emergent mania patients with bipolar disorder”
		Use in children and Effect on human fertility	Deleted as missing information
		Use in patients with renal impairment, Use in patients with hepatic impairment, Use in patients with longer term exposure, Use in patients of different racial or ethnic origin	Added as missing information
			These changes were implemented throughout the RMP.
		Weight gain, Lipid changes, Hyperglycaemia and diabetes mellitus, metabolic risk factors, Somnolence, EPS including TD, Off-label use and misdosing	Inclusion of further guidance on drug administration in the physician leaflet.
2.2	28 Jan 2016	**Important identified risks:** • Extrapyramidal symptoms (EPS) • Somnolence • Weight gain • Lipid changes • Hyperglycaemia and diabetes mellitus	RMP was updated based on Day 55 Comments From The National Agency For Medicines And Medical Devices – Romania dated 03 Nov 2015. The risk profile was adapted to the

Version	Date	Safety Concerns	Comment
		• Metabolic risk factors • Hepatitis with or without jaundice **Important potential risks:** • Cerebrovascular adverse events in elderly • Cerebrovascular adverse events in non-elderly patients • Torsade de Pointes • Ischemic heart disease • Potential for off-label use and misdosing • Abuse and misuse **Missing information:** • Use in pregnant or breast feeding women • Use in patients on concomitant cardiovascular medications • Use in patients on concomitant valproic acid	originator. The safety concerns were updated in Part II Module SVIII, Part V.1, V.3, and VI.1.1 in line with SmPC and PL. Part VI.2.4 Summary of safety concerns was updated for safety concerns in line with SmPC and PL. The updated SmPC and PL were included under Annex 2. Worldwide marketing authorization was updated in Annex 3.