VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Schizophrenia:

Schizophrenia is a serious brain illness. Many people with schizophrenia are disabled by their symptoms. Anyone can develop schizophrenia. It affects men and women equally in all ethnic groups. Teens can also develop schizophrenia. In rare cases, children have the illness, too[1].

Several factors may contribute to schizophrenia, including:

- Genes, because the illness runs in families
- The environment, such as viruses and nutrition problems before birth
- Different brain structure and brain chemistry

Studies with original data related to the prevalence of schizophrenia (published 1965-2002) were identified via searching electronic databases, reviewing citations, and writing to authors. Cumulative plots of prevalence estimates were made and the distributions described when the underlying estimates were sorted according to prevalence type (point, period, lifetime, and lifetime morbid risk). Based on combined prevalence estimates, the influence of selected key variables was examined (sex, urbanicity, migrant status, country economic index, and study quality). A total of 1,721 prevalence estimates from 188 studies were identified. These estimates were drawn from 46 countries, and were based on an estimated 154,140 potentially overlapping prevalent cases. Total 132 core studies, 15 migrant studies, and 41 studies were identified based on other special groups. The median values per 1,000 persons (10%-90% quantiles) for the distributions for point, period, lifetime, and lifetime morbid risk were 4.6 (1.9-10.0), 3.3 (1.3-8.2), 4.0 (1.6-12.1), and 7.2 (3.1-27.1), respectively. Based on combined prevalence estimates, there was no significant difference found (a) between males and females, or (b) between urban, rural, and mixed sites. The prevalence of schizophrenia in migrants was higher compared to native born individuals: the migrant-to-native-born ratio median (10%-90% quantiles) was 1.8 (0.9-6.4). When sites were grouped by economic status, prevalence estimates from ‘‘least developed’’ countries were significantly lower than those from both ‘‘emerging’’ and ‘‘developed’’ sites ($p = 0.04$). Studies that scored higher on a quality score had significantly higher

prevalence estimates (p = 0.02). There is a wealth of data about the prevalence of schizophrenia. These gradients, and the variability found in prevalence estimate distributions, can provide direction for future hypothesis-driven research[2].

Bipolar Disorder:

Bipolar disorder, also known as manic-depressive illness, is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out daily tasks. Symptoms of bipolar disorder can be severe. They are different from the normal ups and downs that everyone goes through from time to time. Bipolar disorder symptoms can result in damaged relationships, poor job or school performance, and even suicide. However, bipolar disorder can be treated, and people with this illness can lead full and productive lives. Bipolar disorder often appears in the late teens or early adult years. At least half of all cases start before age 25. Some people have their first symptoms during childhood, while others may develop symptoms late in life[3].

In the last two decades, a number of population-based studies were conducted that have estimated the lifetime prevalence of bipolar disorder to be approximately 1%. In 1978, Weissman and Myers published the first epidemiologic survey using research diagnostic criteria. The authors utilized the Schedule for Affective Disorders and Schizophrenia and the Diagnostic Research Criteria (SADS-RDC). Weissman and Myers sampled 1,095 households and identified a lifetime prevalence rate of 0.8% for mania and 0.8% for hypomania. They found that bipolar disorders cluster in the higher socioeconomic classes, with 4.6% in Hollingshead and Redlichs classes 1 and 2, 1% in class 3, 0.9% in class 4, and no cases in class 5. Weissman and collaborators (1996) estimated the rates and patterns of bipolar disorder based on population-based studies that had used similar methodology. Studies from 10 different countries (United States, Canada, Puerto Rico, France, West Germany, Italy, Lebanon, Taiwan, South Korea, and New Zealand) were included. Lifetime prevalence rates for bipolar disorder were consistent among countries. The lowest rate was found in Taiwan (0.3 per 100) and the highest in New Zealand (1.5 per 100). Gender ratios did not differ across countries[4].

Major Depressive Disorder (MDD):

MDD is a serious health problem and will be the second leading cause of burden of disease worldwide by 2030. The annual incidence rate of MDD is about 1% to 8%, as shown by population and primary care based surveys such as the National Comorbidity Survey (NCS), the Epidemiologic Catchment Area Study (ECA), the Stirling County Study, the Lundby Study, the Netherlands Mental Health Survey and Incidence Study (NEMESIS) and the PredictD study. The 6 or 12 month prevalence of mood disorders is about 2% to 12%, while the lifetime prevalence is about 4% to 17%. MDD is a debilitating illness and has major personal and public consequences. To be able to prevent MDD, insight into risk factors for the onset of MDD is of clear importance[5].

The average lifetime and 12-month prevalence estimates of DSM-IV MDE were 14.6% and 5.5% in the ten high-income countries (Belgium, France, Germany, Israel, Italy, Japan, Netherland, New Zealand, Spain and United States), and 11.1% and 5.9% in the eight low- to middle-income countries (Brazil, Colombia, India, Lebanon, Mexico, South Africa, Ukraine and PRC). The average age of onset ascertained retrospectively was 25.7 in the high-income and 24.0 in low- to middle-income countries. Functional impairment was associated with recency of MDE. 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. The strongest demographic correlation in high-income countries was being separated from a partner, and in low- to middle-income countries, it was being divorced or widowed[6].

VI.2.2 Summary of treatment benefits

Clinical efficacy and safety studies were not conducted for the proposed product for evaluating effective and safe use of quetiapine, considering this is a generic medicine (a medicine that is developed to be the same as a reference medicine that has already been authorized). The available medical literature is considered sufficient to evaluate the safety of quetiapine in the proposed therapeutic indication(s) for Quetiapine Fumarate prolonged-release tablets. Based on literature data,

proposed tablets are clearly expected to show treatment benefits in schizophrenia, bipolar disorder and major depressive disorder.

VI.2.3 Unknowns relating to treatment benefits

The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies, do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions, including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, new-borns should be monitored carefully.

Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made on whether to discontinue breast-feeding or to discontinue quetiapine therapy, taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and, if required, it should be replaced with a non-inducer (e.g. sodium valproate)

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Nervous system disorders • Extrapyramidal symptoms (inability to initiate movement, inability to remain motionless) • Somnolence (sleepiness)	Quetiapine Amneal in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed	Yes, patients should inform their doctor if they notice any nervous system disorders suns as inability to move properly or excess sleepiness while taking Quetiapine Amneal
Metabolism and nutritional disorders • Weight gain • Lipid changes (fat changes) • Hyperglycaemia and diabetes mellitus (high blood sugar or diabetes) • Metabolic risk factors (alterations in the way your body functions)	In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies	Yes, given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate.

Important potential risks:

Risk	What is known
Nervous system disorders • Cerebrovascular adverse events in elderly • Cerebrovascular adverse events in non-elderly patients (Problems with the blood vessels in the brain or stroke)	An approximately 3-fold increased risk of strokes has been seen in clinical tails. Quetiapine should be used with caution in patients who had stroke, or other conditions predisposing to blood pressure problems. It has been showed that patients taking Quetiapine are at risk of developing such problems especially the elderly.

Risk	What is known
Cardiac disorders • Torsade de Pointes • Ischaemic heart disease (Heart problems)	Cases of heart problems, palpitations, sudden unexplained death, heart failure and heart attacks have been reported with the use of neuroleptics and are considered class effects.
General disorders • Potential for off-label use and misdosing • Psychiatric disorders / injury, poisoning, procedural and complications • Abuse and misuse (Harm caused by taking the wrong amount of medicine or for the wrong purpose)	As quetiapine has several uses, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered. Long-term efficacy and safety in patients with MDD has not been evaluated In general, reported signs and symptoms of overdose those resulting from an exaggeration of the active substance's known pharmacological effects, i.e., drowsiness and sedation, increased heart beats and low blood pressure. Quetiapine is not approved for the treatment of dementia-related psychosis

Missing information:

Risk	What is known
Use in pregnant or breast feeding women	The moderate amount of published data from use during pregnancies (i.e. between 300-1000 pregnancies) do not suggest an increased risk of harm to the foetus due to treatment. However, based on all available data a conclusion cannot be drawn. Animal studies have shown reproductive problems. Therefore, quetiapine is not recommended during pregnancy. Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk. There have been reports of agitation, difficulty moving, tremor, sleepiness, breathing problems, or feeding disorder. Consequently, new-borns should be monitored carefully. Based on very limited data regarding quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent
Use in patients on concomitant cardiovascular medications (Use in patients that take hearth medicines)	Interaction studies with commonly used cardiovascular medicinal products have not been performed

Risk	What is known
Use in patients on concomitant valproic acid	The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of alterations in the white blood cells in the combination group versus the monotherapy groups.

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

The Summary of Product Characteristics (SPC) of quetiapine 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). All these risk minimization measures are given in SPC and PIL of Quetiapine Amneal Prolonged-release Tablets.

No additional risk minimization measures have been proposed for this generic medicine.

VI.2.6 Planned Post-Authorisation Development Plan

No post-authorisation study is planned for this product.

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

Version	Date (dd-mm-yyyy)	Safety Concerns	Comment
01	29 July 2015	*Important identified risks*: • Hypersensitivity to the active substance or to any of the excipients • Extrapyramidal symptoms • Concomitant administration of cytochrome P450 3A4 inhibitors • Somnolence and dizziness • Patients with cardiovascular disease • QT Prolongation	Initial submission

		• Severe Neutropenia • Tardive Dyskinesia • Weight gain • Hyperglycaemia • Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol • Withdrawal symptoms *Important potential risks*: • Neuroleptic Malignant Syndrome • Suicide/suicidal thoughts or clinical worsening • Cerebrovascular adverse events • Use in Fertility, pregnancy and lactation • Use in patients over 65 years • Use in patients with hepatic impairment • Thromboembolism *Missing information*: • Use in Children and Adolescents	
02	1 July 2016	*Important identified risks*: Nervous system disorders • Extrapyramidal symptoms (EPS) • Somnolence Metabolism and nutritional disorders • Weight gain • Lipid changes • Hyperglycaemia and diabetes mellitus	

		• Metabolic risk factors *Important potential risks*: Nervous system disorders • Cerebrovascular adverse events in elderly • Cerebrovascular adverse events in non-elderly patients Cardiac disorders • Torsade de Pointes • Ischaemic heart disease General disorders • Potential for off-label use and misdosing • Psychiatric disorders / injury, poisoning, procedural and complications • 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	