VI. SUMMARY OF THE RISK MANAGEMENT PLAN

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Overview of Disease Epidemiology

Adults

Schizophrenia and Related Disorders

Olanzapine is indicated for the acute and maintenance treatment of schizophrenia and related psychotic disorders. In controlled clinical trials, olanzapine was found to improve both positive and negative symptoms.

Olanzapine has been shown to be effective in maintaining the clinical improvement during 1-year of continuation therapy in patients who have shown an initial treatment response.

Schizophrenia is a group of severe brain disorders in which people interpret reality abnormally. Schizophrenia may result in some combination of hallucinations, delusions, and disordered thinking and behavior.

Contrary to some popular belief, schizophrenia isn't split personality or multiple personality. The word "schizophrenia" does mean "split mind," but it refers to a disruption of the usual balance of emotions and thinking.

Schizophrenia is a chronic condition, requiring lifelong treatment.

By using precise methods in its diagnosis and a large, representative population, the incidence rate of schizophrenia seems consistent across the world for the last half-century. Schizophrenia affects around 0.3–0.7% of people at some point in their life, or 24 million people worldwide as of 2011 (about one of every 285).

Despite the received wisdom that schizophrenia occurs at similar rates worldwide, its prevalence varies across the world, within countries, and at the local and neighborhood level. It causes approximately 1% of worldwide disability-adjusted life years (DALYs). The rate of schizophrenia varies up to threefold depending on how it is defined.

Each year, one in 10,000 people age 12 to 60 develops schizophrenia. It is diagnosed 1.4 times more frequently in males than females and typically appears earlier in men—the peak ages of onset are 20–28 years for males and 26–32 years for females. Onset in childhood is much rarer, as is onset in middle- or old age.

Generally, the mean age of first admission for schizophrenics is between 25 and 35. Studies have suggested that lower income individuals tend to have their disorder diagnosed later after the onset of symptoms, relative to those of better economic standings. As a result, the lower social classes are more likely to be living with their illness untreated. One recovery center in the United States reported that 92% of its clients received government benefits because their income fell below the poverty line. These statistics show that a number of people suffering from mental illnesses are a part of disenfranchised and impoverished groups, and are therefore unable to attain the adequate healthcare they need in order to effectively treat their mental disorders.

It is generally accepted that women tend to present with schizophrenia anywhere between 4-10 years after their male counterparts. However, using broad criteria for diagnosing schizophrenia shows that males have a bimodal age of onset, with peaks at 21.4 years and 39.2 years old, while females have a trimodal age of onset with peaks at at 22.4, 36.6, and 61.5 years old.

Bipolar Disorder

Olanzapine is indicated for the acute treatment of manic or mixed episodes in bipolar disorder. Olanzapine may be used as monotherapy or cotherapy with agents commonly used in the treatment of acute bipolar disorder (e.g., lithium or divalproex sodium).

The efficacy of olanzapine as monotherapy maintenance treatment in bipolar patients with manic or mixed episodes who responded to acute treatment with olanzapine was demonstrated in two 1-year “time to relapse” trials.

The physician who elects to use olanzapine for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Bipolar disorder — sometimes called manic-depressive disorder — is associated with mood swings that range from the lows of depression to the highs of mania. When you become depressed, you may feel sad or hopeless and lose interest or pleasure in most activities. When your mood shifts in the other direction, you may feel euphoric and full of energy. Mood shifts

may occur only a few times a year, or as often as several times a day. In some cases, bipolar disorder causes symptoms of depression and mania at the same time.

Although bipolar disorder is a disruptive, long-term condition, you can keep your moods in check by following a treatment plan. In most cases, bipolar disorder can be controlled with medications and psychological counseling (psychotherapy).

About 4% of people have one of the types of bipolar disorder at some point in their life. Lifetime prevalence of bipolar disorder type I, which includes at least one manic episode during a lifetime, has generally been estimated at 2%. 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). Including sub-threshold diagnostic criteria, such as one or two symptoms over a short time-period, an additional 5.1% of the population, adding up to a total of 6.4%, were classified as having a bipolar spectrum disorder. A more recent analysis of data from a second US National Comorbidity Survey found that 1% met lifetime prevalence criteria for bipolar I, 1.1% for bipolar II, and 2.4% for subthreshold symptoms. There are conceptual and methodological limitations and variations in the findings. Prevalence studies of bipolar disorder are typically carried out by lay interviewers who follow fully structured/fixed interview schemes; responses to single items from such interviews may suffer limited validity. In addition, diagnoses (and therefore estimates of prevalence) vary depending on whether a categorical or spectrum approach is used. This consideration has led to concerns about the potential for both underdiagnosis and overdiagnosis.

Rates are similar in men and women and, broadly, across different cultures and ethnic groups. A 2000 study by the World Health Organization found that prevalence and incidence of bipolar disorder are very similar across the world. Age-standardized prevalence per 100,000 ranged from 421.0 in South Asia to 481.7 in Africa and Europe for men and from 450.3 in Africa and Europe to 491.6 in Oceania for women. However, severity may differ widely across the globe. Disability-adjusted life year rates, for example, appear to be higher in developing countries, where medical coverage may be poorer and medication less available.

Within the United States, African and European Americans have similar rates of bipolar disorder, while Asian Americans have lower rates.

Late adolescence and early adulthood are peak years for the onset of bipolar disorder. One study also found that in 10% of bipolar cases, the onset of mania had happened after the patient had turned 50.

Summary of existing efficacy data

Often there is a generalization about whether second-generation antipsychotic agents are superior to first-generation antipsychotic agents in treating schizophrenia and other psychotic illnesses. Neither second- nor first-generation antipsychotic agents form a homogeneous class as they differ in many properties (eg, efficacy, side effects, cost, and pharmacology). The benefit-risk ratio must be kept in constant perspective because each antipsychotic agent is also associated with serious adverse side effects, which are important in outcome measures.

The atypical antipsychotics (AAP) (also known as second generation antipsychotics) are a group of antipsychotic tranquilizing drugs used to treat psychiatric conditions. Olanzapine is approved for use in the treatment of schizophrenia and related psychotic disorders. In controlled clinical trials, olanzapine was found to improve both positive and negative symptoms.

Both generations of medication tend to block receptors in the brain's dopamine pathways, but atypicals at the time of marketing were claimed to differ from typical antipsychotics in that they are less likely to cause extrapyramidal motor control disabilities in patients, which include unsteady Parkinson's disease-type movements, body rigidity and involuntary tremors. During the course of treatment atypical antipsychotics are associated with the following benefits:

- higher rate of responders, efficiency in patients with refractory disease,
- lower risk of suicides,
- better functional capacity and an improved quality of life.

Summary of safety concerns

The followings are considered as safety concerns related to olanzapine:

Risk	**What is known**	**Preventability**
Risk in patients with	Olanzapine is contraindicated in patients with eye	These risks can be prevented

known risk of narrow angle glaucoma	problems such as certain kinds of glaucoma (increased pressure in the eye).	by respecting the product information.
Risk of increase in mortality and risk of cerebrovascular event	The use of olanzapine in elderly patients with dementia is not recommended as it may have serious side effects. If the patient suffer from dementia, he (she) or the carer/relative should tell the doctor if he (she) has ever had a stroke or "mini" stroke.	These risks can be prevented by respecting the product information.
Risk of worsening of Parkinsonian symptoms and hallucinations	Patients who suffer from Parkinson's disease, should tell the doctor as soon as possible.	These risks can be prevented by respecting the product information.
Risk of Neuroleptic Malignant Syndrome (NMS)	Very rarely, medicines of this type cause a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness.	These risks can be prevented by respecting the product information.
Risk of hyperglycaemia and diabetes	High blood sugar have been seen in patients taking olanzapine. Your doctor should do blood tests to check blood sugar before you start taking olanzapine and regularly during treatment.	These risks can be prevented by respecting the product information.
Risk of lipid alterations	High levels of fat (triglycerides and cholesterol) have been seen in patients taking olanzapine. Your doctor should do blood tests to check certain fat levels before you start taking olanzapine and regularly during treatment.	These risks can be prevented by respecting the product information.
Risk of hepatic toxicity	If you suffer from liver disease, the doctor should be informed. Other additional side effects for which a frequency cannot be estimated from the available data (not known) include liver disease appearing as yellowing of the skin and white parts of the eyes	These risks can be prevented by respecting the product information.
Risk of neutropenia	Caution should be exercised in patients with blood disorders.	These risks can be prevented by respecting the product information.
Risk of discontinuation symptoms	Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported very rarely (<0.01%) when olanzapine is stopped abruptly.	These risks can be prevented by respecting the product information.
Risk of QTc prolongations	As with other antipsychotics, caution should be	These risks can be prevented

	exercised when olanzapine is prescribed in patients with heart disease	by respecting the product information.
Risk of seizures	Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur rarely in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.	These risks can be prevented by respecting the product information.
Risk of tardive dyskinesia	Medicines of this type may cause unusual movements mainly of the face or tongue; if these signs or symptoms appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.	These risks can be prevented by respecting the product information.
Risk of postural hypotension in the elderly	As a routine precaution, it is recommended that blood pressure is measured periodically in patients over 65 years. In the early stages of treatment, some people may feel dizzy or faint (with a slow heart rate), especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, the doctor should be called.	These risks can be prevented by respecting the product information.
Risk of sudden cardiac death	Other additional side effects for which a frequency cannot be estimated from the available data (not known) include sudden unexplained death.	These risks can be prevented by respecting the product information.
Risk of weight gain, changes in metabolic parameters and increase in prolactin levels in paediatric population	Weight gain has been seen in patients taking olanzapine. The doctor should check patients' weight regularly.	These risks can be prevented by respecting the product information.

Risk	**What is known**
Risk of venous thromboembolism (VTE)	Medicines like these have been associated with the formation of blood clots.
Effects of general CNS activity, when taken in combination with other centrally acting medicines and	Caution should be used when olanzapine is

alcohol	taken in combination with other centrally acting medicines and alcohol, as together with alcohol it may cause drowsiness.
Potential interaction with specific CYP1A2 inhibitors such as fluvoxamine and ciprofloxacin	If the patient is also taking carbamazepine (an anti-epileptic and mood stabiliser), fluvoxamine (an antidepressant), or ciprofloxacin (an antibiotic) - it may be necessary to change the olanzapine dose.

Risk	**What is known**
Use in pregnant and lactating women	*Pregnancy* Patients should be advised to notify their doctor if they become pregnant or intend to become pregnant during treatment with olanzapine. The following symptoms may occur in newborn babies, of mothers that have used olanzapine 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. *Breast feeding* Olanzapine was excreted in breast milk.Patients should be advised not to breast feed an infant if they are taking olanzapine.
Use in children with long-term treatment	Olanzapine is not indicated for use in the treatment of children and adolescents.
Risk of anticholinergic related events	Patients who suffer from a blocked intestine (Paralytic ileus), prostate problems should tell their doctor as soon as possible.

Summary of risk minimisation activities by safety concern

Routine pharmacovigilance activities are considered enough to cover all risks. All safety concerns presented in the section above are known for olanzapine and other similar medicinal products and they are described in the proposed product information. These risks can be prevented or their severity can be limited by following the instructions in the summary of product characteristics and package leaflet.

Planned post-authorisation development plan

None.

Summary of changes to the risk management plan over time

Not applicable.