

Part VI. SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. Elements for Summary Tables in the EPAR

VI.1.1. Summary Table of Safety Concerns

Table 49. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Extrapyramidal syndrome including Tardive dyskinesia QT Prolongation Serotonin syndrome
Important potential risks	Hyperprolactinemia Increased cerebrovascular events in elderly patients with dementia-related psychosis Increased mortality in elderly patients with dementia-related psychosis Neuroleptic malignant syndrome Suicidality
Important missing information	Pregnant and lactating women

VI.1.2. Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

There are no ongoing or planned studies in the post-authorization pharmacovigilance development plan.

VI.1.3. Summary of Post-Authorisation Efficacy Development Plan

There is no post-authorization efficacy development plan.

VI.1.4. Summary Table of Risk Minimisation Measures

Beyond routing risk minimization, there are no risk minimization measures for this RMP.

VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Ziprasidone belongs to a group of medicines called antipsychotic drugs that treat schizophrenia in adult patients and bipolar disorders in adult patients and children in Europe.

Ziprasidone is available as an IM injectable for rapid control of acute agitation in schizophrenia patients for whom treatment with ziprasidone is appropriate, for up to 3 days. It is also available as capsules and oral suspension for the long-term treatment, prevention of relapse during continuation therapy, and treatment of bipolar disease manic or mixed episodes.

Schizophrenia is diagnosed 1.4 times more frequently in males than in females. In men, symptoms of schizophrenia most often appears earlier in men, around ages 20–28 years and in women, around ages 26–32 years.^{183,184} In childhood, schizophrenia is much rarer, with onset in middle- or old age.¹⁸⁵

The highest impact of schizophrenia tends to be in Oceania, the Middle East, and East Asia. The lowest impact tends to be in the nations of Australia, Japan, the United States, and most of Europe, as of 2000.¹⁸⁵

It is not clear how antipsychotic drugs, like ziprasidone work or treat schizophrenia and bipolar disease. These drugs are helpful for patients who have abnormal thoughts, see and hear things that are not there, are agitated, and have happy and sad periods, with depression.

Common side effects include difficulty swallowing, stiff muscles and joints and difficulty moving; sometimes have slower movement of the body; sleepiness, and may have allergic reactions such as rash.

Clinical studies have demonstrated the safety and efficacy of ziprasidone for the treatment of schizophrenia and bipolar disorders. Post-marketing safety data supports the effectiveness and safety of ziprasidone.

Ziprasidone has been marketed for many years and its usefulness has been well established for the approved indications.

VI.2.2. Summary of Treatment Benefits

Ziprasidone belongs to a group of medicines called atypical antipsychotics or second-generation antipsychotics (SGAs) that work by their effect on multiple aspects of brain chemistry. Ziprasidone oral formulations are indicated for the management of schizophrenia and other psychotic disorders and for the maintenance of clinical improvement and prevention of relapse during continuation therapy. There is also an intramuscular formulation for the treatment of acute agitation. It is also indicated for the treatment of manic or mixed episodes associated with bipolar disorder in adults, children, and adolescents aged 10 to 17 years.

Ziprasidone has been marketed for many years and its usefulness has been well-established for the approved indications.

VI.2.3. Unknowns Relating to Treatment Benefits

There is no new information related to the treatment benefits.

VI.2.4. Summary of Safety Concerns

Table 50. Important Identified Risks

Risk	What is Known	Preventability
Extrapyramidal syndrome including Tardive dyskinesia	Extrapyramidal syndrome is a class effect of antipsychotic medications that involves a group of symptoms includes, but is not limited to movement disorders, dystonic effects. Tardive dyskinesia occurs with chronic dosing of antipsychotic medications.	Physician management and care. Periodic physical examination.
QT Prolongation	QT prolongation is a class effect of antipsychotic medications that can occur with repeated, chronic dosing.	Physician management and care. Conduct of ECG prior to and periodic ECG during

Table 50. Important Identified Risks

Risk	What is Known	Preventability
		long-term treatment.
Serotonin syndrome	Serotonin syndrome is a class effect of antipsychotic medications that can occur with repeated, chronic dosing.	Physician management and care.

Table 51. Important Potential Risks

Risk	What is Known
Hyperprolactinemia	Increases in the hormone prolactin may occur. It can cause enlargement of the breast, male sexual dysfunction and no menstrual period. All of the antipsychotic drugs have this side effect.
Increased cerebrovascular events in elderly patients with dementia-related psychosis	There can be a higher number of cerebrovascular events, including stroke, when antipsychotic medications are given to older patients with dementia-related psychosis. All of the antipsychotic drugs have this side effect.
Increased mortality in elderly patients with dementia-related psychosis	There can be a higher number of fatal outcomes when antipsychotic medications are given to older patients with dementia-related psychosis. All of the antipsychotic drugs have this side effect.
Neuroleptic malignant syndrome	Neuroleptic malignant syndrome is an antipsychotic class effect that occurs with chronic, repeated dosing.
Suicidality	Suicide thoughts, attempts to commit suicide or committing suicide are related to schizophrenia and bipolar disease. Some of the risk factors associated with high risk for suicide issues in patients diagnosed with schizophrenia include, but are not limited to, mental deterioration, agitation or restlessness, and not taking their antipsychotic medicines.

Table 52. Missing Information

Risk	What is Known
Pregnancy and Lactation	The use of ziprasidone in pregnant women and breastfeeding has not been studied. Children who are exposed to antipsychotic drugs during the later part of pregnancy may have extrapyramidal symptoms.

VI.2.5. Summary of Risk Minimisation Measures by Safety Concern

All medicines have a SmPC which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the PIL. The measures in these documents are known as routine risk minimisation measures. No additional risk minimisation measures are proposed.

Table 53. QT/QTc Prolongation

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of QT/QTc Prolongation
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Other side effects that affect the heart may occur due to the lengthening of the QT interval during an electrocardiogram test• Management of patients closely for cardiac symptoms• Patient Leaflet informs the patient about the expected side effects and communicating with their physician

Table 54. Extrapyramidal Syndrome, Including Tardive Dyskinesia

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of Extrapyramidal Symptoms, including Tardive dyskinesia
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Management of patients closely for abnormal muscle movement, stiffness or inability to move; difficulty swallowing or talking; Patient Leaflet informs the patient about the expected side effects and communicating with their physician

Table 55. Serotonin Syndrome

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of Serotonin Syndrome
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Management of patients closely for agitation or restlessness; confusion; rapid heart rate and high blood pressure; dilated pupils; loss of muscle coordination or twitching muscles; muscle rigidity, abnormal muscle aches and pain; heavy sweating; diarrhoea; and especially, high fever, seizures, irregular heartbeat, unconsciousness.• Patient Leaflet informs the patient about the expected side effects and communicating with their physician

Table 56. Hyperprolactinemia

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of Hyperprolactinemia
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Monitor serum prolactin levels• Patient Leaflet informs the patient about the expected side effects and communicating with their physician

Table 57. Increased Cerebrovascular Effects, Including Stroke in Elderly Patients with Dementia-Related Psychosis

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of Increased Cerebrovascular Effects, including stroke in elderly patients with dementia-related psychosis
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Management of patients closely for changes in consciousness, balance, speech changes, seizures, change in limb movement and facial changes symptoms• Patient Leaflet informs the patient about the expected side effects and communicating with their physician

Table 58. Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of Increased mortality in elderly patients with dementia-related psychosis
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Management of patients closely for cardiac or organ system failure symptoms• Conduct routine laboratory test in line with standard of care• Patient Leaflet informs the patient about the expected side effects and communicating with their physician

Table 59. Neuroleptic Malignant Syndrome

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of Neuroleptic Malignant Syndrome
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Management of patients closely for fever, muscle stiffness, pain or weakness; feeling hot• Conduct testing of urine, CPK; body temperature• Patient Leaflet informs the patient about the expected side effects and communicating with their physician

Table 60. Suicidality

Risk Minimisation Measure(s): Healthcare Professional and Patient Education
Objective and rationale: Patients and HCPs to understand the risk of Suicidality
Healthcare Provider educational materials are provided to prescribing physicians and pharmacists including advice on: <ul style="list-style-type: none">• Management of patients closely for changes in perception, attitude, behaviour, adherence to antipsychotic, mood stabilizing and antidepressant medications; increased or sudden depression; ideas about committing suicide or ending their life; sudden changes in their life• Conduct physical examination to look for signs of attempting to hurt themselves• Patient Leaflet informs the patient about the expected side effects and communicating with their physician

VI.2.6. Planned Post-Authorisation Development Plan

The RMP has been updated to indicate the studies providing data on long-term effects on growth, learning and memory, and sexual maturation in paediatric subjects have been finalized and published. The data in 2 studies with combined data of 30 weeks of continuous ziprasidone treatment has not demonstrated any indication of long-term effects of ziprasidone on the growth, learning and memory and sexual maturation in pediatric patients since the last RMP update in 2010. Data from the post-marketing safety data has not provided any additional data on the long-term effects in pediatric subjects taking ziprasidone for longer than 30 weeks however, the data is limited to market authorization in the EU, where ziprasidone is approved for the treatment of pediatric patients diagnosed with Bipolar disorder. No additional risk minimization activities are planned.

Studies that are a Condition of the Marketing Authorisation

There are no studies that are required as a condition of the Marketing Authorization.

VI.2.7. Summary of Changes to the Risk Management Plan Over Time

No changes have been made to the Risk Management Plan.