PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris (Ziprasidone)

This is a summary of the risk management plan (RMP) for ziprasidone. The RMP details important risks of Ziprasidone, how these risks can be minimised, and how more information will be obtained about Ziprasidone's risks and uncertainties (missing information).

Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how it should be used.

I. The Medicine and What it is Used For

Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris is authorised for:

Management of schizophrenia and other psychotic disorders, and for maintenance of clinical improvement and prevention of relapse during continuation therapy.

Treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features.

Rapid control of agitation in psychotic patients

Treatment of manic or mixed episodes of moderate severity in bipolar disorder in children and adolescents aged 10-17 years.

It contains ziprasidone as the active substances and can be given orally via oral capsules containing ziprasidone hydrochloride monohydrate equivalent to 20, 40, 60 or 80 mg ziprasidone. Oral suspension containing ziprasidone hydrochloride monohydrate equivalent to 10 mg ziprasidone per mL. Ziprasidone mesylate for injection, equivalent to 20 mg of ziprasidone per mL, following reconstitution (Powder for solution for intramuscular injection).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris, together with measures to minimise such risks and the proposed studies for learning more about Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the public (e.g. with or without prescription) can help to minimises its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken by patients. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine/use in special patient populations etc.);

Table 1: Part VI.1- Summary of Safety Concerns

List of Important Risks and Missing Information	
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
Missing Information	• Pregnant and lactating women

II.B Summary of Important Risks

Table 2: Part VI.2- Important Identified Risk -Extrapyramidal Syndrome Including Tardive Dyskinesia

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	The risk of EPS increases at higher doses. Risks factors vary for different symptoms but can relate to age and gender as well as the presence of certain co-morbidities. For some of the most common symptoms, risk factors have been reported as follows: • Acute dystonia: young age, female gender, history of a substance use disorder, family history of dystonia. • Parkinsonism: advance age, female gender, cognitive deficits, early onset EPS.

	• Tardive dyskinesia: months to years of use, increased age, non-Caucasian, female, history of diabetes, organic brain damage, presence of negative symptoms of schizophrenia.
Risk Minimisation Measures	Routine risk minimisation measures SmPC sections 4.4, 4.6, 4.8 PIL section 4 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 3: Part VI.2- Important Identified Risk - QT Prolongation

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Ziprasidone is contraindicated in patients with: • Known QT interval prolongation including congenital long QT Syndrome • Recent myocardial infarction • Uncompensated heart failure • Cardiac arrhythmias requiring treatment with Class IA and III antiarrhythmic drugs; no public health impact. QT prolongation can be related to other physiological conditions or medications. Risk factors for the development of drug-induced QT prolongation and TdP include medications that are associated with prolongation of the QT interval (e.g. antibiotics; certain antidepressant and antipsychotic medication; some antihistamines; diuretics; Class I and III antiarrhythmic medications; HMG CoA reductase inhibitors; certain diabetes medications); congenital defects; low potassium, magnesium or calcium blood levels; increasing age; female gender; genetic predisposition (e.g. family history of sudden death; history of previous drug-induced QT prolongation; congenital long QT syndrome); impaired elimination due to renal or hepatic disease; congenital long QT syndrome; absolute or relative bradycardia; hypothermia; and abnormal thyroid function
Risk Minimisation Measures	Routine risk minimisation measures SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8 PIL sections 2 and 4 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 4: Part VI.2- Important Identified Risk - Serotonin Syndrome

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and

	spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Patients receiving more than one serotonergic medication in addition to ziprasidone, as well as recent initiation or increased dose of medication known to increased serotonin levels, or over-the-counter medications, illicit
Risk Minimisation Measures	Routine risk minimisation measures SmPC sections 4.5, 4.8 PIL section 4 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 5: Part VI.2- Important Potential Risk – Hyperprolactinaemia

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Patients taking antipsychotic medications, particularly women treated with antipsychotic medication;[1],[2] pregnancy; development of certain neoplasms (e.g. prolactin-secreting hormones)[3]; patients diagnosed with pituitary disease, primary hypothyroidism, chronic renal failure, hypothalamic disease, cirrhosis, as well as neurogenic and idiopathic causes.
Risk Minimisation Measures	Routine risk minimisation measures SmPC sections 4.4, 4.8 PIL section 4 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 6: Part VI.2- Important Potential Risk – Increased Cerebrovascular Events in Elderly Patients with Dementia-related Psychosis

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Elderly patients with dementia-related psychosis may be at increased risk for CVA.
Risk Minimisation Measures	Routine risk minimisation measures SmPC section 4.4 PIL section 2 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 7: Part VI.2- Important Potential Risk – Increased Mortality in Elderly Patients with Dementia-related Psychosis

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Patients with dementia-related psychosis are at increased risk for a fatal outcome.
Risk Minimisation Measures	Routine risk minimisation measures SmPC section 4.4 PIL section 4 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 8: Part VI.2- Important Potential Risk – Neuroleptic Malignant Syndrome

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	NMS is typically caused by exposure to neuroleptic/antipsychotic medications and can occur at therapeutic doses. The risk may increase at higher doses or with rapid dose increases and in the presence of more than 1 neuroleptic/antipsychotic medication. In addition, other risk factors that can contribute to the development of NMS include nearly all dopamine antagonists, in particular high potency antipsychotics, compared to a lower risk with atypical antipsychotics and low potency antipsychotic medications; prior NMS episodes (in 15% - 20% of the cases), withdrawal from levodopa or dopamine agonists. Patient with catatonia may also be at risk of developing NMS.
Risk Minimisation Measures	Routine risk minimisation measures SmPC section 4.4. 4.8 PIL section 4 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 9: Part VI.2- Important Potential Risk – Suicidality

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Suicide related events may be due to underlying conditions in patients receiving ziprasidone.

Risk Minimisation Measures	Routine risk minimisation measures None. Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

Table 10: Part VI.2- Important Missing Information – Pregnant and Lactating Women

Evidence for Linking the Risk to the Medicine	Based on data derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature and due to the possible undesirable clinical outcomes related to it, this safety concern has been classified as an important identified/potential risk.
Risk Factors and Risk Groups	Not applicable
Risk Minimisation Measures	Routine risk minimisation measures SmPC section 4.6 PIL section 3 Additional risk minimisation measures Not applicable as there are no additional risk minimisation measures for this safety concern

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Geodon®/Zeldox®, Ziprasidon Upjohn/Ziprasidon Viatris.