Part V: Part VI: Summary of the risk management plan

Summary of risk management plan for <Invented name> 25 mg & 100 mg tablets (Clozapine)

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

<Invented name>'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how <invented name> should be used.

Important new concerns or changes to the current ones will be included in updates of <invented name>'s RMP.

I. The medicine and what it is used for

Treatment-resistant schizophrenia

<Invented name> is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

Psychosis during the course of Parkinson’s disease

<Invented name> is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed. It contains clozapine as the active substance and it is given orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of <invented name>, together with measures to minimise such risks and the proposed studies for learning more about <invented name>'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 patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, 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 <invented name> is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of <invented name> are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 <invented name>. 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);

List of important risks and missing information	
Important identified risks	• Agranulocytosis • Seizures/convulsions • Cardiovascular events - myocarditis, cardiomyopathy, myocardial infarction, orthostatic hypotension) • Neuroleptic malignant syndrome • Thromboembolism • Metabolic changes including weight gain, diabetes mellitus, dyslipidemia • QT-prolongation • Hepatotoxicity
Important potential risks	• Cerebrovascular events in elderly with dementia • Sudden death • Renal failure • Rebound, withdrawal effects
Missing information	• Use in pregnant and lactating patients • Use in children and adolescents

II.B Summary of important risks

Important identified risk: Agranulocytosis	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.3, 4.4, 4.8, 5.1 Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: Educational material for HCPs and patients.

Important identified risk: Seizures/convulsions	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.4, 4.5, 4.7 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Important identified risk: Cardiovascular events - myocarditis, cardiomyopathy, myocardial infarction, orthostatic hypotension	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.3, 4.4, 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: Educational material for HCPs and patients.

Important identified risk: Neuroleptic malignant syndrome	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4, 4.5, 4.8. Other routine risk minimisation measures beyond the Product Information:

	• Prescription Only Medicine Additional risk minimisation measures: None.

Important identified risk: Thromboembolism	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4, 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Important identified risk: Metabolic changes including weight gain, diabetes mellitus, dyslipidemia	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.4, 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Important identified risk: QT-prolongation	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4, 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Important identified risk: Hepatotoxicity	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Important potential risk: Cerebrovascular events in elderly with dementia	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Important potential risk: Sudden death	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Important potential risk: Renal failure	
Risk minimisation measures	Routine risk minimisation measures SmPC section 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine

	Additional risk minimisation measures: None.

Important potential risk: Rebound, withdrawal effects	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2, 4.4, 4.6, 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Missing information: Use in pregnant and lactating patients	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.6, 4.8. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

Missing information: Use in children and adolescents	
Risk minimisation measures	Routine risk minimisation measures SmPC sections 4.2. Other routine risk minimisation measures beyond the Product Information: • Prescription Only Medicine Additional risk minimisation measures: None.

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 <invented name>.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for <invented name>.