Part VI: Summary of the risk management plan

Summary of risk management plan for Serdolect (sertindole)

The RMP details important risks of Serdolect, how these risks can be minimised, and how more information will be obtained about Serdolect's risks and uncertainties (missing information).

Serdolect’s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Serdolect should be used.

Important new concerns or changes to the current ones will be included in updates of Serdolect 's RMP.

I. The medicine and what it is used for

Serdolect is authorised for treatment of schizophrenia in patients intolerant to at least one other antipsychotic agent. Sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients. (see SmPC for the full indication). It contains sertindole as the active substance and it is given by film-coated tablets of 4, 12, 16 and 20 mg.

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

Important risks of Serdolect, together with measures to minimise such risks and the proposed studies for learning more about Serdolect'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 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 the case of Serdolect, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment (which has as of 2020 a frequency of 3 years) 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 Serdolect is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Serdolect 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 Serdolect. 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	Sudden Cardiac Death

List of important risks and missing information	
	Torsade de Pointes / QT Prolongation (SMQ) Cardiac Arrhythmias (HLGT) Co-administration with drugs that prolong the QT interval Co-administration of drugs that inhibit CYP3A or 2D6
Important potential risks	None
Missing information	Safety in pregnancy and lactation

II.B Summary of important risks

Table Part VI.1 Summary of important risks

Important identified risk: Sudden Cardiac Death	
Evidence for linking the risk to the medicine	Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Prolongation of the QTc interval is associated with the ability to cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death.
Risk factors and risk groups	Suicide associated with severe mental illness Substance abuse Comorbid physical conditions Adverse events of medication including drug interactions
Risk minimisation measures	<u>Routine risk minimisation measures</u>: Text in SmPC section 4.2, 4.3, 4.4, 4.5 and 5.3. Prescription-only medicine in a restricted indication and with special precautions. <u>Additional risk minimisation measures</u>: Direct Healthcare Professional Communication – DHPC Educational material
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities</u>: See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Torsade de Pointes / QT Prolongation (SMQ)	
Evidence for linking the risk to the medicine	Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Prolongation of the QTc interval is associated with the ability to

	cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death.
Risk factors and risk groups	- use of sertindole in the highest dose ranges - congenital or acquired history of QT prolongation - cardiovascular disease including bradycardia - female gender - electrolyte imbalances (hypomagnesaemia, hypokalaemia) - co-administration of drugs which prolong the QT interval - co-administration of drugs that inhibits the metabolism of sertindole - severe hepatic impairment
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC section 4.2, 4.3, 4.4, 4.5, 4.8 and 5.3. Prescription-only medicine in a restricted indication and with special precautions. Additional risk minimisation measures: Direct Healthcare Professional Communication – DHPC Educational material
Additional pharmacovigilance activities	Additional pharmacovigilance activities: See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Cardiac Arrhythmias (HLGT)	
Evidence for linking the risk to the medicine	Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Prolongation of the QTc interval is associated with the ability to cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death.
Risk factors and risk groups	Smoking, overweight/obesity, hyperlipidaemia, physical inactivity, diabetes, gender, age, ethnic origin, family history and mental illness.
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC section 4.2, 4.3, 4.4, 4.5, 4.8 and 5.3. Prescription-only medicine in a restricted indication and with special precautions. Additional risk minimisation measures: Direct Healthcare Professional Communication – DHPC Educational material

Additional pharmacovigilance activities	Additional pharmacovigilance activities: See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Co-administration with drugs that prolong the QT interval	
Evidence for linking the risk to the medicine	Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Any concomitant medication that increases the serum concentration, does increase the risk that QT prolongation occurs.
Risk factors and risk groups	Patients who are prescribed a high dose of sertindole are at risk.
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC section 4.3, 4.4, 4.5 and 4.9. Prescription-only medicine in a restricted indication and with special precautions. Additional risk minimisation measures: Direct Healthcare Professional Communication – DHPC
Additional pharmacovigilance activities	Additional pharmacovigilance activities: See section II.C of this summary for an overview of the post-authorisation development plan.
Important identified risk: Co-administration of drugs that inhibit CYP3A or 2D6	
Evidence for linking the risk to the medicine	Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Inhibition of CYP3A or 2D6 may lead to an increased serum level of sertindole (Murdoch 2006), which may lead to prolongation of the QTc interval, which is associated with the ability to cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death.
Risk factors and risk groups	Patients who are prescribed a high dose of sertindole are at risk.
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC section 4.3, 4.4 and 4.5. Prescription-only medicine in a restricted indication and with special precautions. Additional risk minimisation measures: Direct Healthcare Professional Communication – DHPC

Additional pharmacovigilance activities	Additional pharmacovigilance activities: See section II.C of this summary for an overview of the post-authorisation development plan.
Missing information: Safety in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: Text in SmPC section 4.6 and 4.8. Prescription-only medicine in a restricted indication and with special precautions. Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies were conditions of the marketing authorisation:

- Drug Utilisation Databases (DUD) studies (17169N)

Purpose of the study: To better understand the usage of sertindole after its return to the market and to relate this usage to potential safety issues.

These studies were discontinued due to poor patient uptake in the databases and hence for these studies it is very unlikely to add any further knowledge to the safety profile of sertindole. This conclusion by Lundbeck was supported by the PRAC in the Final PSUR Assessment Report of 03 September 2020.

- Observational study on ECG compliance (14290A)

Purpose of the study: To study prescribers' adherence with the SPC requirements for ECG monitoring to minimise the risk of QT interval prolongation and cardiac disorders

This study was completed in2017 and the final study report for study 14290A was submitted to the Danish Medicines Agency as well as to the countries that were part of the Mutual Recognition Procedure (MRP).

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

There are no further studies required for Serdolect.