Summary of risk management plan for Spectrila (recombinant L-asparaginase)

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

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

This summary of the RMP for Spectrila should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

Spectrila is authorised for the treatment of adults and children with acute lymphoblastic leukaemia (see SmPC for the full indication). It contains asparaginase produced in *Escherichia coli* cells by recombinant DNA technology as the active substance and it is administered intravenously.

Further information about the evaluation of Spectrila's benefits can be found in Spectrila's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/spectrila.

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

Important risks of Spectrila, together with measures to minimise such risks and the proposed studies for learning more about Spectrila'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 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 events is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Spectrila are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. 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 Spectrila. 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	– Severe hypersensitivity reactions – Decreased asparaginase activity – Pancreatitis
Important potential risks	– Potential interaction of vincristine and L-asparaginase
Missing information	– None

II.B Summary of important risks

Important identified risk: Severe hypersensitivity reactions	
Evidence for linking the risk to the medicine	Clinical trials with Spectrila (MC-ASP.5/ALL) and literature
Risk factors and risk groups	Unknown
Risk minimisation measures	*Routine risk minimisation measures* SmPC sections 4.3, 4.4, and 4.8 SmPC section 4.4: No administration of Spectrila as a bolus intravenous injection SmPC section 4.4: Use of a previous intracutaneous test or a small intravenous test dose SmPC section 4.4: Immediate discontinuation of administration of Spectrila in case of allergic symptoms SmPC section 4.4: Appropriate treatment may include antihistamines and corticosteroids PL sections 2, and 4 The PL includes similar information in lay language. Spectrila is available on prescription only. *Additional risk minimisation measures* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* MC-Spectrila.1/ALL See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Decreased asparaginase activity	
Evidence for linking the risk to the medicine	Clinical trials with Spectrila (MC-ASP.5/ALL)
Risk factors and risk groups	Unknown
Risk minimisation measures	*Routine risk minimisation measures* SmPC sections 4.2, 4.3, and 4.4 SmPC sections 4.2, and 4.4: Monitoring of serum asparaginase activity

Important identified risk: Decreased asparaginase activity	
	measured three days after administration of Spectrila; a switch to a different asparaginase preparation should be considered, if asparaginase activity values fail to reach target levels. SmPC section 4.4: Expert advice is recommended prior to switching to a different asparaginase preparation. rASNase is available on prescription only. *Additional risk minimisation measures* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* MC-Spectrila.1/ALL See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Pancreatitis	
Evidence for linking the risk to the medicine	Clinical trials with Spectrila and literature
Risk factors and risk groups	Patients with severe hypertriglyceridaemia are at an increased risk for the development of acute pancreatitis.
Risk minimisation measures	*Routine risk minimisation measures* SmPC sections 4.3, 4.4, and 4.8 SmPC section 4.4: Monitoring of blood levels of pancreatic enzymes and lipids; treatment discontinuation in patients developing acute pancreatitis; these patients should no longer be treated with any asparaginase preparation PL sections 2, and 4 rASNase is available on prescription only. *Additional risk minimisation measures* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* MC-Spectrila.1/ALL See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Potential interaction of vincristine and L-asparaginase	
Evidence for linking the risk to the medicine	Experimental studies in dogs
Risk factors and risk groups	Unknown
Risk minimisation measures	*Routine risk minimisation measures* SmPC section 4.5 PL section 2 SmPC sections 4.5: Vincristine should be given 3 to 24 hours before administration of asparaginase in order to minimise toxicity. The PL includes similar information in lay language. rASNase is available on prescription only. *Additional risk minimisation measures* None

Important potential risk: Potential interaction of vincristine and L-asparaginase	
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* MC-Spectrila.1/ALL See section II.C of this summary for an overview of the post-authorisation development plan.

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 Spectrila.

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

MC-Spectrila.1/ALL

Purpose of the study:

The experience with recombinant L-asparaginase in adult patients with acute lymphoblastic leukaemia is limited. Therefore, the applicant committed to conduct a post-authorisation efficacy and safety study in this population.

The primary objective of this study is the assessment of induction phase response, defined as subjects with asparaginase activity trough levels in serum ≥ 100 U/L in induction phase. Secondary objectives include asparaginase activity trough levels in serum in induction phase. Tertiary objectives include the assessment of consolidation phase response, assessment of asparaginase activity trough levels in serum in consolidation phase II, asparagine levels in serum and cerebrospinal fluid, complete remission status and minimal residual disease status, immunogenicity (incl. anti-asparaginase antibodies), and safety.