Stemline®
A Menarini Group Company

Elzonris® (Tagraxofusp)
Konzentrat zur Herstellung einer Infusionslösung, 1mg/ml
Zul.-Nr. 68’797

Public Risk Management Plan (RMP) Summary

Version 1.0 (Feb 2023) based on EU-RMP V2.2

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of Elzonris® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of Elzonris® in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Stemline Therapeutics Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of Elzonris®.

Part VI: Summary of the risk management plan for ELZONRIS (tagraxofusp)

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

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

This summary of the RMP for ELZONRIS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 ELZONRIS's RMP.

I. The medicine and what it is used for

ELZONRIS is authorised as monotherapy for the treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) (see SmPC for the full indication). ELZONRIS is a diphtheria toxin- interleukin-3 (IL-3) fusion protein produced by recombinant DNA technology in Escherichia coli. ELZONRIS is composed of the catalytic and transmembrane domains of Corynebacterium diphtheriae toxin fused via a Met-His linker to IL-3 as the active substance and it is as an intravenous infusion.

Further information about the evaluation of ELZONRIS's benefits can be found in ELZONRIS EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage. *Elzonris EPAR.*

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

Important risks of ELZONRIS, together with measures to minimise such risks and the proposed studies for learning more about ELZONRIS'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 the case of ELZONRIS, 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 - 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 ELZONRIS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ELZONRIS 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 ELZONRIS. 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);

Table II. A: Important risks and missing information

List of important risks and missing information	
Important identified risks	Capillary leak syndrome
Important potential risks	Hepatotoxicity Choroid Plexus Lesions
Missing information	Use in patients with hepatic impairment Use in patients with severe renal impairment Use in patients with significant cardiovascular history Drug interaction data

II.B Summary of important risks

Table II.B. 1: Important identified risk - Capillary leak syndrome

Evidence for linking the risk to the medicine	Overall 18% (32/176) of patients treated with ELZONRIS monotherapy at ≤12 µg/kg/day experienced CLS, with a similar incidence among BPDCN patients (20% [18/89]). Most CLS events were Grade 2 in intensity. CLS was Grade 3 and Grade 4 in intensity for 6 and 2 patients, respectively. For 3 patients with BPDCN, CLS was Grade 5 (i.e., had a fatal outcome). Of the 27 patients for whom CLS was not fatal or did not lead to ELZONRIS discontinuation, only 1 patient experienced a recurrence of CLS when retreated with ELZONRIS.
Risk factors and risk groups	Symptoms of CLS include hypoalbuminemia, weight increase, oedema and hypotension
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2, 4.4 and 4.8 PIL sections 2 and 4 SmPC section 4.4 where advice is given on management of CLS Additional risk minimisation measures: Healthcare Professional Guide Patient Alert Card
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up questionnaire for adverse reaction Additional pharmacovigilance activities: Post-authorisation (*safety and efficacy study conducted via a*) Registry of ELZONRIS (tagraxofusp), with primary objective to assess the incidence of CLS

Table II.B. 2: Important potential risk - Hepatotoxicity

Evidence for linking the risk to the medicine	The most common treatment-emergent adverse events (TEAEs) among BPDCN patients were liver transaminase elevations. Among BPDCN patients, 66% (59/89) experienced ALT increased and 53 (60%) experienced AST increased. For 30 patients, ALT increased and/or AST increased were Grade 3 in intensity; 2 Grade 4 cases were reported. Most cases of ALT increased and AST increased were transient, resolving within a cycle. Furthermore, most cases were non-serious, with 2 BPDCN patients experiencing serious ALT increased and/or AST increased.
Risk factors and risk groups	Patients presenting with underlying elevated liver enzymes can be susceptible to further liver function abnormalities if not managed adequately.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 and 4.8 PIL section 4

Additional pharmacovigilance activities	Routine pharmacovigilance: AE follow-up questionnaire for adverse reaction Additional pharmacovigilance activities: Post-authorisation (*safety and efficacy study conducted via a*) Registry of ELZONRIS (tagraxofusp) to collect additional information on these missing data.

Table II.B. 3: Important potential Risk - Choroid Plexus Lesions

Evidence for linking the risk to the medicine	Inflammation and necrosis of epithelial cells lining the choroid plexus were observed across some animal studies, and particularly at high doses in studies MPI-2231-002 and MPI-2231-007. This observation was consistent with previous nonclinical toxicity studies preceding the first-in-human investigator-sponsored clinical trial. Importantly, there was no documented evidence suggestive of choroid plexitis on neuroimaging in any of the Nervous system disorder serious treatment related cases. Additionally, there were no serious nor severe adverse reactions suggestive of idiopathic raised intracranial pressures in the 176 patients who received ELZONRIS at ≤12 µg/kg/day. A toxicity biomarker related to ELZONRIS for the development of choroid plexus lesions has not been identified. Changes in the choroid plexus may be of relevance to humans. No neurological events occurred on study 0114 in BPDCN patients that are considered related to choroid plexus deposits.
Risk factors and risk groups	Risk is unknown
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 PIL section 4
Additional pharmacovigilance activities	Additional pharmacovigilance activities: PASS (non-clinical) to determine a potential toxicity biomarker to further investigate the risk of 'choroid plexus lesions'. Post-authorisation (*safety and efficacy study conducted via a*) Registry of ELZONRIS (tagraxofusp) to collect additional information on these missing data. The study design will be revised to include additional safety monitoring for choroid plexitis.

Table II.B. 4: Missing information - Use in patients with hepatic impairment

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and 5.2
Additional pharmacovigilance activities	Routine pharmacovigilance: AE follow-up questionnaire for adverse reaction Additional pharmacovigilance activities: Post-authorisation (*safety and efficacy study conducted via a*) Registry of ELZONRIS (tagraxofusp) to collect available information on these missing data.

Table II.B. 5: Missing information – Use in patients with severe renal impairment

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and 5.2
Additional pharmacovigilance activities	Routine pharmacovigilance: AE follow-up questionnaire for adverse reaction Additional pharmacovigilance activities: Post-authorisation (*safety and efficacy study conducted via a*) Registry of ELZONRIS (tagraxofusp) to collect available information on these missing data.

Table II.B. 6: Missing information – Use in patients with significant cardiovascular history

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.2 and 4.4
Additional pharmacovigilance activities	Routine pharmacovigilance: AE follow-up questionnaire for adverse reaction Additional pharmacovigilance activities: Post-authorisation (*safety and efficacy study conducted via a*) Registry of ELZONRIS (tagraxofusp) to collect available information on these missing data.

Table II.B. 7: Missing information – Drug interaction data

Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.5
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

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

Short study name: Post-authorisation (*safety and efficacy study conducted via a*) Registry of ELZONRIS (tagraxofusp).

Purpose of the study: A non-interventional category 2 PASS with study aims to assess the clinical outcomes (primarily the rate of Complete response after 3 months +/- 1 month) and incidence of capillary leak syndrome (CLS) in patients actively treated for BPDCN in routine practice compared to clinical studies. Secondary objectives will include: Rate bridge to stem cell transplant (SCT), Progression-free survival, Overall survival, Best Overall Response, Duration of Response, , Dose interruptions and/or the administration of intravenous albumin supplementation in patients presenting with a diagnosis or symptoms of CLS (i.e. hypoalbuminemia, oedema, weight gain and/or hypotension), Incidence and severity ofAdverse Events of Special Interest, Describe available safety data of tagaxofusp monotherapy in patients with significant cardiovascular history, hepatic impairment and/or renal impairment, and Evaluate number of doses/cycles administered. Choroid plexitis will be included as an adverse event of special interest.

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

Study short name: Immunohistochemistry staining of brain tissue samples from Study MPI 2231 007.

Purpose of the study: A category 3 post-authorisation non-clinical study on Blood Brain Barrier (BBB) models will be conducted in order to determine a potential toxicity biomarker to further investigate the risk of 'choroid plexus lesions'. As described in SVII.1.2, the risk and impact of choroid plexus lesions (including choroid plexitis) identified in non-clinical studies has not been fully characterized nor quantified. Although there were no serious cases of raised intracranial pressure with unaccounted etiology, cases where neuroimaging was performed may not have specifically included review of choroid plexus morphology/pathology. A nonclinical approach is proposed for a greater understanding of potential mechanisms of the choroid plexus findings from the tagraxofusp cynomologus monkey toxicology studies. This nonclinical study will explore the ability of tagraxofusp to cross the BBB as a means of investigating the development of choroid plexitis observed in some animals. Data obtained may provide insight into potential biomarkers of this toxicity or additional information on potential mechanisms. Until that time, all ICSRs will be collected as assessed in accordance with routine PV activities.