ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

ELZONRIS 1 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL of concentrate for solution for infusion contains 1 mg tagraxofusp. Each vial contains 1 mg of tagraxofusp.

Tagraxofusp is a diphtheria toxin-interleukin-3 (IL-3) fusion protein produced by recombinant DNA technology in *Escherichia coli*.

Excipient with known effect

Each vial contains 50 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Clear, colourless liquid. A few white to translucent particles may be present.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELZONRIS is indicated as monotherapy for the first-line treatment of adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN) (see section 5.1).

4.2 Posology and method of administration

ELZONRIS should be administered under the supervision of a physician experienced in the use of anti-cancer agents. Appropriate resuscitation equipment should be available.

Posology

The recommended dose is 12 mcg/kg tagraxofusp administered as an intravenous infusion over 15 minutes, once daily, on days 1-5 of a 21-day cycle. The dosing period may be extended for dose delays up to day 10 of the cycle. Treatment should be continued until disease progression or unacceptable toxicity (see section 4.4).

First treatment cycle
The first cycle of ELZONRIS should be administered in the in-patient setting. Patients should be monitored for signs and symptoms of hypersensitivity or capillary leak syndrome (see section 4.4) until at least 24 hours after the last infusion.

Subsequent treatment cycles

ELZONRIS can be administered in the in-patient setting or in a suitable out-patient ambulatory care setting that is equipped for intensive monitoring of patients with haematopoietic malignancies undergoing treatment.

Pre-medication
Patients should be pre-medicated with a H1-histamine antagonist (e.g. diphenhydramine hydrochloride), a H2-histamine antagonist, a corticosteroid (e.g. 50 mg intravenous methylprednisolone or equivalent) and paracetamol approximately 60 minutes prior to the start of infusion (see section 4.4).

Dose adjustments

Vital signs should be monitored and albumin, transaminases, and creatinine checked prior to preparing each dose of ELZONRIS. See Table 1 for recommended dose modifications and Table 2 for capillary leak syndrome (CLS) management guidelines.

Vital signs should be monitored frequently during dosing.

Table 1: Recommended ELZONRIS dosing regimen modifications

Parameter	**Severity criteria**	**Dose modification**
Serum albumin	Serum albumin < 3.5 g/dL or reduced ≥ 0.5 g/dL from value measured prior to initiation of the current cycle	See CLS Management Guidelines (Table 2)
Body weight	Body weight increase ≥ 1.5 kg over pre-treatment weight on prior treatment day	See CLS Management Guidelines (Table 2)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	ALT or AST increase > 5 times the upper limit of normal	Withhold treatment until transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 micromol/L) or creatinine clearance < 60 mL/minute	Withhold treatment until serum creatinine resolves to ≤ 1.8 mg/dL (159 micromol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	Withhold treatment until systolic blood pressure is < 160 mmHg or > 80 mmHg.
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	Withhold treatment until heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38 °C	Withhold treatment until body temperature is < 38 °C.
Hypersensitivity reactions	Mild or moderate	Withhold treatment until resolution of any mild or moderate hypersensitivity reaction. Resume ELZONRIS at the same infusion rate.

Table 2: CLS management guidelines

Time of Presentation	**CLS Sign/Symptom**	**Recommended Action**	**ELZONRIS Dosing Management**
Prior to first dose of ELZONRIS in cycle 1	Serum albumin < 3.2 g/dL	Administer ELZONRIS when serum albumin ≥ 3.2 g/dL	
During ELZONRIS dosing	Serum albumin < 3.5 g/dL	Administer 25 g intravenous albumin every 12 hours (or more frequently as practical) until serum albumin is ≥ 3.5 g/dL AND not reduced by	Hold dosing until the relevant CLS sign/symptom

Time of Presentation	CLS Sign/Symptom	Recommended Action	ELZONRIS Dosing Management
	Serum albumin reduced by ≥ 0.5 g/dL from the albumin value measured prior to ELZONRIS dosing initiation of the current cycle	≥ 0.5 g/dL from the value measured prior to dosing initiation of the current cycle	has resolved [1]
	A pre-dose body weight that is increased by ≥ 1.5 kg over the previous day's pre-dose weight	Administer 25 g intravenous albumin (every 12 hours or more frequently as practical), and manage fluid status as indicated clinically (e.g., generally with intravenous fluids and vasopressors if hypotensive and with diuretics if normotensive or hypertensive), until body weight increase has resolved (i.e. the increase is no longer ≥ 1.5 kg greater than the previous day's pre-dose weight).	
	Oedema, fluid overload and/or hypotension	Administer 25 g intravenous albumin (every 12 hours, or more frequently as practical) until serum albumin is ≥ 3.5 g/dL. Administer 1 mg/kg of methylprednisolone (or an equivalent) per day, until resolution of CLS sign/symptom or as indicated clinically. Aggressive management of fluid status and hypotension if present, which could include intravenous fluids and/or diuretics or other blood pressure management, until resolution of CLS sign/symptom or as clinically indicated.	

[1] If ELZONRIS dose is held:

- ELZONRIS administration may resume in the same cycle if all CLS signs/symptoms have resolved and the patient did not require measures to treat haemodynamic instability.
- Administration should be held for the remainder of the cycle if CLS signs/symptoms have not resolved or the patient required measures to treat haemodynamic instability (e.g., required administration of intravenous fluids and/or vasopressors to treat hypotension) (even if resolved).
- Administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is haemodynamically stable.

Special populations

Renal impairment
No data are available for patients with renal impairment (see section 5.2).

Hepatic impairment
No data are available for patients with hepatic impairment (see section 5.2).

Elderly
No dose adjustment is required for patients over 65 years of age (see section 5.2). Generally, safety was similar between elderly patients (≥ 65 years of age) and patients less than 65 years of age treated with ELZONRIS.

Paediatric population

The safety and efficacy of ELZONRIS in children and adolescents below 18 years have not been established (see section 5.1).
No data are available.
Method of administration

ELZONRIS is for intravenous use.

The prepared dose of diluted ELZONRIS should be administered via an infusion syringe pump over 15 minutes. The total infusion time should be controlled using an infusion syringe pump to deliver the entire dose and the sodium chloride 9 mg/mL (0.9%) solution for injection within 15 minutes.

ELZONRIS must not be administered as an intravenous push or bolus. It should be administered through a dedicated intravenous line and it must not be mixed with other medicinal products (see section 6.2).

Prior to infusion, venous access should be established and maintained with sodium chloride 9 mg/mL (0.9%) solution for injection.

For instructions on preparation and administration of the medicinal product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Capillary leak syndrome
Capillary leak syndrome (CLS), including life-threatening and fatal cases have been reported with most events occuring during the first five days of the first cycle of treatment. The most frequent signs and symptoms of CLS included weight increased, hypoalbuminemia and hypotension. The incidence of weight increased, hypoalbuminemia, hypotension, and blood alkaline phosphatase increased are all higher among patients who experienced CLS compared to patients that did not experience CLS. Renal failure and acute kidney injury have been reported in two patients with BPDCN and in one patient with AML secondary to CLS (see section 4.8).

Before initiating therapy, ensure that the patient has adequate cardiac function and serum albumin ≥ 3.2 g/dL. During treatment, regularly monitor serum albumin levels prior to the initiation of each dose, or more often as clinically indicated. Additionally, assess patients for other signs/symptoms of CLS including weight gain, new onset or worsening oedema, including pulmonary oedema, and hypotension including haemodynamic instability (see Table 2).

Patients should be made aware of identifying CLS symptoms and when to seek immediate medical attention. Intravenous albumin supplementation and dosing interruptions may be required (see section 4.2).

Hypersensitivity reactions
Severe hypersensitivity reactions have been reported with ELZONRIS. Commonly reported reactions include rash (generalised / maculo-papular); wheezing; pruritus; angioedema; swelling face; and flushing (see section 4.8). Monitor patients for hypersensitivity reactions during treatment. Depending on the severity and the required interventions, temporarily withhold treatment and resume after symptoms have resolved (see section 4.2).

Haematological abnormalities

Thrombocytopenia and neutropenia have been reported in patients treated with ELZONRIS monotherapy (see section 4.8). The majority of events were reported in cycle 1 and cycle 2 of treatment, were not dose-limiting and did not recur in subsequent cycles. Patients should be routinely monitored and treated as clinically indicated.

Tumour lysis syndrome
ELZONRIS can cause tumour lysis syndrome (TLS), which may be fatal as a result of its rapid anti-tumour activity (see section 4.8).

Identify TLS based on clinical presentation and symptoms, including acute renal failure, hyperkalaemia, hypocalcaemia, hyperuricaemia, or hyperphosphataemia from tumour lysis. Patients considered at high risk for TLS due to high tumour burden should be managed as clinically indicated, including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care.

Hepatotoxicity
Treatment with ELZONRIS has been associated with elevations in liver enzymes (see section 4.8). Acute hepatic failure and liver encephalopathy has been reported in a patient treated with ELZONRIS at a higher dose (16 mcg/kg). During treatment, regularly monitor ALT and AST levels prior to the initiation of each dose. Temporarily withhold treatment if transaminases rise to greater than 5 times the upper limit of normal and resume treatment when transaminase elevations are ≤ 2.5 times the upper limit of normal (see section 4.2).

Choroid plexus lesions
Choroid plexitis was identified during non-clinical studies (see section 5.3). While not observed in clinical studies, if clinical symptoms or signs suggestive of central nervous system (CNS) damage occur, full clinical and neuro-imaging examination, including fundoscopy and brain magnetic resonance imaging, is recommended.

CNS-involved BPDCN
The passage of tagraxofusp through the blood brain barrier is unknown. Other treatment alternatives should be considered if CNS disease is present.

Women of childbearing potential/contraception
In women of childbearing potential, a negative pregnancy test should be obtained within 7 days prior to initiation of therapy. Effective contraception should be used before the first dose is administered and for at least one week after the last dose.

Hereditary fructose intolerence
Patients with hereditary fructose intolerance (HFI) must not be given this medicinal product unless strictly necessary.

A detailed history with regard to HFI symptoms has to be taken of each patient prior to being given this medicinal product.

Sodium sensitivity
This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

In women of childbearing potential, a negative pregnancy test should be obtained within 7 days prior to initiation of therapy. Effective contraception should be used before the first dose is administered and for at least one week after the last dose.

Pregnancy
There are no data from the use of ELZONRIS in pregnant women.
Animal reproduction studies have not been conducted with tagraxofusp (see section 5.3).

ELZONRIS should not be used during pregnancy unless the clinical condition of the woman requires treatment with tagraxofusp.

Breast-feeding
It is unknown whether tagraxofusp/metabolites are excreted in human milk.
A risk to breast-feeding newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with ELZONRIS and for at least one week after the last dose.

Fertility
No fertility studies have been conducted with tagraxofusp (see section 5.3). There are no data on the effect of tagraxofusp on human fertility.

4.7 Effects on ability to drive and use machines

ELZONRIS has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse reaction that may occur during ELZONRIS treatment is CLS (see sections 4.2 and 4.4) which was reported in 18% of patients with a median time to onset of CLS of 6 days.

Adverse reactions occurring in ≥ 20% of patients treated with ELZONRIS were hypoalbuminemia, increased transaminases, thrombocytopenia, nausea, fatigue and pyrexia.

Adverse reactions grade 3 and above according to the Common Terminology Criteria for Adverse events (CTCAE) and occurring in > 5% of patients were increased transaminases, thrombocytopenia and anaemia.

Tabulated list of adverse reactions

The adverse reaction frequency is listed by MedDRA System Organ Class (SOC) at the preferred term level. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000 to < 1/100).

The adverse reactions described in this section were identified in clinical studies of patients with haematologic malignancies (N=176), including 89 patients with BPDCN. In these studies, ELZONRIS was administered as monotherapy at doses of 7 mcg/kg (12/176, 7%), 9 mcg/kg (9/176, 5%) and 12 mcg/kg (155/176, 88%). Incidence and severity of adverse reaction in patients with BPDCN were similar to those of the entire studied population.

Table 3: Tabulated list of adverse reactions by MedDRA System Organ Class

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
Infections and infestations	**Common** Cellulitis **Uncommon** Pneumonia Urinary tract infection Gingivitis	None
Blood and lymphatic system disorders	**Very Common** Thrombocytopenia Anaemia **Common** Febrile neutropenia Neutropenia Leukopenia Leukocytosis Lymphopenia	**Very Common** Thrombocytopenia **Common** Febrile neutropenia Anaemia Neutropenia Leukopenia Lymphopenia **Uncommon** Leukocytosis
Immune system disorders	**Common** Cytokine release syndrome	**Uncommon** Cytokine release syndrome
Metabolism and nutrition disorders	**Very Common** Hypoalbuminemia **Common** Decreased appetite Tumour lysis syndrome Hyperglycaemia Hyperuricaemia Hypocalcaemia Hypomagnesaemia Hyponatraemia Hypokalaemia Hyperkalaemia Hyperphosphataemia **Uncommon** Hypophosphataemia Lactic acidosis Acidosis	**Common** Tumour lysis syndrome Hyperglycaemia Hypoalbuminemia Hyponatraemia **Uncommon** Hyperuricaemia Hypocalcaemia Hypokalaemia Lactic acidosis Acidosis
Psychiatric disorders	**Common** Confusional state **Uncommon** Anxiety Depression Insomnia Mental status changes	None
Nervous system disorders	**Common** Syncope Headache Dizziness **Uncommon** Encephalopathy Metabolic encephalopathy Cerebrovascular accident Facial paralysis Dysgeusia Multiple sclerosis relapse Somnolence Paraesthesia Parosmia Peripheral motor neuropathy Peripheral sensory neuropathy	**Common** Syncope **Uncommon** Cerebrovascular accident Metabolic encephalopathy
Eye Disorders	**Common**	None

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
	Vision blurred **Uncommon** Conjunctival haemorrhage Ocular hyperaemia Vitreous floaters	
Cardiac Disorders	**Common** Pericardial effusion Tachycardia Sinus tachycardia **Uncommon** Ventricular fibrillation Supraventricular extrasystoles Atrial fibrillation Bradycardia Myocardial infarction	**Uncommon** Ventricular fibrillation Pericardial effusion Sinus tachycardia Myocardial infarction
Vascular disorders	**Very Common** Capillary leak syndrome Hypotension[a] **Common** Flushing **Uncommon** Hypertension Haematoma	**Common** Capillary leak syndrome Hypotension
Respiratory, thoracic and mediastinal disorders	**Common** Hypoxia Pulmonary oedema Dyspnoea Epistaxis Pleural effusion Cough **Uncommon** Respiratory failure Wheezing Oropharyngeal pain Tachypnoea	**Common** Hypoxia Pulmonary oedema **Uncommon** Respiratory failure Dyspnoea
Gastrointestinal Disorders	**Very Common** Nausea Vomiting **Common** Dysphagia Diarrhoea Stomatitis Dyspepsia Dry mouth Constipation **Uncommon** Abdominal distension Abdominal pain Gingival bleeding Tongue blistering Tongue haematoma	**Uncommon** Nausea
Hepatobiliary disorders	**Common** Hyperbilirubinemia	None
Skin and subcutaneous tissue disorders	**Common** Pruritus Rash[b] Hyperhidrosis Petechiae **Uncommon** Angioedema	**Uncommon** Angioedema Rash

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
	Swelling face Palmar-plantar erythrodysesthesia syndrome Urticaria Alopecia Pain of skin Stasis dermatitis Cold sweat Dry skin	
Musculoskeletal and connective tissue disorders	**Common** Back pain Bone pain Myalgia Arthralgia Pain in extremity Muscular weakness **Uncommon** Musculoskeletal pain Coccydynia Muscle spasms Rhabdomyolysis	**Uncommon** Back pain Arthralgia Rhabdomyolysis
Renal and urinary disorders	**Common** Acute kidney injury **Uncommon** Renal failure Urinary retention Urinary tract pain Pollakiuria Proteinuria	**Uncommon** Acute kidney injury
General disorders and administration site conditions	**Very Common** Pyrexia Chills Fatigue[c] Oedema peripheral[d] **Common** Influenza-like illness Chest pain Pain Malaise **Uncommon** Drug intolerance Hypothermia Systemic inflammatory response syndrome	**Common** Fatigue **Uncommon** Pyrexia Chills Oedema peripheral Drug intolerance
Investigations	**Very Common** Transaminases increased[e] Weight increased **Common** Electrocardiogram QT prolonged Blood alkaline phosphatase increased Blood creatinine increased Blood lactate dehydrogenase increased Blood creatine phosphokinase increased Activated partial thromboplastin time prolonged International normalised ratio increased **Uncommon** Blood fibrinogen decreased Bacterial test positive Weight decreased	**Very Common** Transaminases increased **Uncommon** Electrocardiogram QT prolonged Blood lactate dehydrogenase increased Bacterial test positive

MedDRA System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 and above
Injury, poisoning and procedural complications	**Common** Infusion related reaction Contusion	**Uncommon** Infusion related reaction

[a] Includes procedural hypotension, orthostatic hypotension

[b] Includes rash pustular, rash maculo-papular, rash erythematous, rash generalised, rash macular

[c] Includes asthenia, lethargy

[d] Includes generalised oedema, oedema, peripheral swelling, fluid retention, fluid overload, periorbital oedema, hypervolaemia

[e] Includes ALT/AST increased, liver function test increased, hepatic enzyme increased

Description of selected adverse reactions

Capillary leak syndrome
Capillary leak syndrome was reported in 18% (32/176), with 12% (21/176) Grade 2, 3% (6/176) Grade 3, 1% (2/176) Grade 4, and fatal in 1.7% (3/176). Of the 25 patients that resumed treatment after experiencing an event of CLS, only 1 patient experienced a recurrence of CLS. The median time to onset of CLS was short (6 days), with all but 2 patients experiencing the first onset of CLS in cycle 1. No patient experienced the first onset of CLS after cycle 2. The overall incidence of CLS was similar in patients with BPDCN (20%, 18/89), including 12% (11/89) Grade 2, 2% Grade 3 (2/89), 2% Grade 4 (2/89) and 3 fatal cases (3%). Patients are required to have adequate cardiac function prior to administration of ELZONRIS (see sections 4.2 and 4.4).

Hepatotoxicity
ALT and AST elevations were reported as adverse reactions in 47% (83/176) and 46% (81/176) of patients treated with ELZONRIS monotherapy, respectively. ≥ Grade 3 ALT and AST increased were reported in 23% (40/176) and 23% (40/176), respectively. Elevated liver enzymes occurred in the majority of patients in cycle 1 and were reversible following dose interruptions (see section 4.4). Similar onset time and incidence were observed in patients with BPDCN, with 51% (45/89) of patients experiencing adverse events of ALT and AST elevations, with ≥ Grade 3 ALT and AST increased reported in 28% (25/89) and 29% (26/89) respectively. Two patients with BPDCN met the laboratory criteria for Hy's Law; in both cases the laboratory abnormalities were noted during Cycle 1.

Haematological abnormalities
Thrombocytopenia was reported in 30% (53/176) of patients treated with ELZONRIS monotherapy and in 35% (31/89) of patients with BPDCN. Thrombocytopenia Grade ≥ 3 was reported in 23% (40/176) of patients treated with ELZONRIS monotherapy and in 26% (23/89) of patients with BPDCN. The majority of thrombocytopenia events were reported in cycle 1 and cycle 2 of treatment. Neutropenia was reported in 9% (15/176) of patients treated with ELZONRIS monotherapy and in 11% (10/89) of patients with BPDCN, with events ≥ Grade 3-reported in 6% (11/176) and 8% (7/89), respectively.

Hypersensitivity
Reactions representative of hypersensitivity were reported in 19% (33/176) of patients treated with ELZONRIS monotherapy and in 17% (15/89) of patients with BPDCN, with events ≥ Grade 3 reported in 3% (6/176) and 4% (4/89), respectively (see section 4.4).

Immunogenicity
Immune response was evaluated by assessment of serum binding reactivity against tagraxofusp (anti-drug antibodies; ADA) and neutralising antibodies by inhibition of functional activity. Immune response was assessed using two immunoassays. The first assay detected reactivity directed against tagraxofusp (ADA), and the second assay detected reactivity against the interleukin-3 (IL-3) portion of tagraxofusp. Two cell-based assays were used to investigate the presence of neutralising antibodies by inhibition of a cell-based functional activity.

In 190 patients treated with ELZONRIS in four clinical studies:

- 94% (176/187) of patients evaluable for the presence of pre-existing ADA at baseline before treatment were confirmed positive with 27% being positive for the presence of neutralising antibodies. The high prevalence of ADA at baseline was anticipated due to diphtheria immunisation.

- 100% (N=170) of patients evaluable for treatment-emergent ADA tested positive with most patients showing an increase in ADA titre by the end of Cycle 2 of ELZONRIS.

- 92% (155/169) of ADA-positive patients evaluable for the presence of neutralising antibodies post-treatment were neutralising antibody-positive.

- 75% (129/171) of patients evaluable for treatment-emergent anti-IL-3 antibodies tested positive with most patients testing positive by Cycle 3 of ELZONRIS.

- 74% (93/126) of patients who tested positive for anti-IL-3 antibodies and were evaluable for the presence of neutralising antibodies were neutralising antibody-positive

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There have been no cases of overdose reported with ELZONRIS. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment provided immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents; other antineoplastic agents,
ATC code: L01XX67

Mechanism of action

Tagraxofusp is a CD123-directed cytotoxin composed of recombinant human interleukin-3 (IL-3) and truncated diphtheria toxin (DT) fusion protein that targets CD123-expressing cells. Tagraxofusp irreversibly inhibits protein synthesis of target cells by inactivating elongation factor 2 (EF2), resulting in apoptosis (cell death).

Clinical efficacy and safety

Study STML-401-0114 was a multi-stage (stage 1 dose escalation, stage 2 expansion, stage 3 confirmatory, stage 4 continued access), non-randomised, open-label, multi-centre study of ELZONRIS. ELZONRIS was administered to 65 previously-untreated and 19 previously treated adult patients with BPDCN according to the WHO classification who received a 12 mcg/kg dose on days 1-5 of multiple 21-day cycles (Table 4). Patients who had known active or suspected CNS leukaemia were not included in the study. The primary endpoint was the rate of complete response (CR; complete resolution of the disease)/clinical complete response (CRc; CR with residual skin abnormality not indicative of active disease). Across all 65 previously untreated patients ELZONRIS resulted in a

CR/CRc rate of 56.9% (95% CI: 44.0, 69.2), this included 13 patients in the confirmatory efficacy cohort where the CR/CRc rate was 53.8% (95% CI: 25.1, 80.8). (Table 5).

Patient baseline characteristics are presented in Table 4 and key efficacy measures in Table 5.

Table 4: Baseline demographics of patients with treatment-naïve BPDCN treated with 12 mcg/kg of ELZONRIS

Parameter	Treatment-naive BPDCN N=65
Gender, N (%)	
Male	52 (80)
Female	13 (20)
Race, N (%)	
White	57 (88)
Other	8 (12)
Age (years)	
Median	68
Minimum, Maximum	22, 84
ECOG, N (%)	
0	31 (48)
1	31 (48)
2	2 (3)
BPDCN at Baseline, N (%)	
Skin	60 (92)
Bone Marrow	32 (49)
Peripheral Blood	17 (26)
Lymph Nodes	33 (51)
Visceral	10 (15)

Table 5: Efficacy measures in patients with treatment-naïve BPDCN treated with 12 mcg/kg of ELZONRIS

Parameter	Confirmatory cohort N=13	Treatment-naive BPDCN N=65
Response rate		
CR/CRc* Rate, N (%)	7 (54)	37 (57)
(95% CI)	(25.1, 80.8)	(44.0, 62.9)
Duration of CR/CRc (months)**		
Median	NE	7.3
Minimum, Maximum	4.7, 28.5	0.7, 49.1
Overall response rate, N (%)	10 (77)	49 (75)
(95% CI)	(46.2, 95.0)	(63.1, 85.2)
Bridge to stem cell transplant		
Rate, N (%)	6 (46)	21 (32)
(95% CI)	(19.2, 74.9)	(21.2, 45.1)
Overall survival		
Median	18.9 (5.2, NE)	12.3 (9.3, 35.9)
Minimum, Maximum	0.2, 28.9	0.2, 49.7

Parameter	Confirmatory cohort N=13	Treatment-naive BPDCN N=65
12-month survival, % (95% CI)	53.8 (24.8, 76.0)	52.2 (38.5, 64.2)
18-month survival, % (95% CI)	53.8 (24.8, 76.0)	48.2 (34.6, 60.5)
24-month survival, % (95% CI)	46.2 (19.2, 69.6)	40.9 (27.5, 53.9)

* CRc is defined as complete response with residual skin abnormality not indicative of active disease.

** Duration of CR/CRc includes patients bridged to stem cell transplantation.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with ELZONRIS in all subsets of the paediatric population in BPDCN (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of tagraxofusp has been evaluated in 43 patients with BPDCN. Most patients (n=38) had pre-existing anti-drug antibodies (ADA) against the diphtheria toxin (DT) component, due to previous vaccination. Pre-existing ADAs resulted in higher clearance and lower tagraxofusp concentrations. During treatment, all patients developed high ADA titres, and substantially reduced free tagraxofusp levels (see below). All data referred to below are based on free tagraxofusp concentrations in BPDCN patients without pre-existing anti-drug antibodies (ADA, n=5) in the first treatment cycle. Descriptive information is included for BPDCN patients with pre-existing ADAs (n=38).

Distribution

Following administration of ELZONRIS 12 mcg/kg via 15-minute infusion in patients with BPDCN without pre-existing anti-drug antibodies (ADA, N=5), the mean (SD) unbound area under the plasma drug concentration over time curve ($AUC_{unbound}$) of free tagraxofusp on Day 1 of the first cycle of treatment (C1D1) was 230 (123) hr*mcg/L and maximum unbound plasma concentration (C_{max}) was 162 (58.1) mcg/L.

The mean (SD) volume of distribution of free tagraxofusp on C1D1 was 5.1 (1.9) L in 4 patients with BPDCN without pre-existing ADA.

Elimination

Tagraxofusp is expected to be degraded into peptides and its constituent amino acids through proteolysis, with no involvement of CYP or transporters.

The mean (SD) clearance of free tagraxofusp at C1D1 was 7.1 (7.2) L/hr in 4 patients with BPDCN without pre-existing ADA, and the mean (SD) terminal half-life of tagraxofusp was 0.7 (0.3) hours.

Anti- drug antibody formation affecting pharmacokinetics

Patients with pre-existing ADA had lower unbound tagraxofusp plasma concentrations (AUC and C_{max}) at C1D1 than patients without pre-existing ADA. Due to the limitation of the bioanalytical method in the presence of ADA, quantitative pharmacokinetic parameters in these patients cannot be given.

Pharmacokinetic/pharmacodynamic relationship

Data collected during Cycle 3 showed increased titres of ADAs and substantially reduced free tagraxofusp concentrations. However, clinical efficacy has been demonstrated beyond Cycle 1 despite the reduced exposure. Due to the limitation of the bioanalytical method, the utility of free tagraxofusp concentrations as a predictor of response is limited.

Pharmacokinetics in special populations
Due to the limitation of the bioanalytical method, the pharmacokinetics of tagraxofusp in patients with renal or hepatic impairment and the effect of body weight, age, and gender are considered unknown.

Paediatric population
The pharmacokinetics of tagraxofusp have not been studied in the paediatric population.

5.3 Preclinical safety data

Carcinogenicity or genotoxicity studies have not been performed with tagraxofusp. Tagraxofusp is a recombinant protein and is therefore not expected to interact directly with DNA.

At human equivalent doses greater than or equal to 1.6 times the recommended dose based on body surface area, severe kidney tubular degeneration/necrosis was observed in cynomolgus monkeys. At human equivalent doses equal to the recommended dose, degeneration/necrosis of the choroid plexus in the brain was observed in cynomolgus monkeys. These findings were generally noted after 5 days of daily dosing. The reversibility of this finding was not assessed at lower doses, but the finding was irreversible and became progressively more severe at a human equivalent dose 1.6 times the recommended dose, 3 weeks after dosing stopped. These findings in kidney and choroid plexus are considered likely relevant for the clinical situation.

No fertility studies have been conducted with tagraxofusp. A literature-based risk assessment suggests that exposure to exogenous IL-3 or blockade of IL-3 signaling may have embryotoxic effects on foetal haematopoiesis and embryo-foetal development. The effects of diphtheria toxin exposure on placental and embryo-foetal development are unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium chloride
Sorbitol (E420)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
3 years.

After opening
From a microbiological point of view, once opened, the medicinal product should be diluted and infused immediately.

After preparation of solution for infusion
Chemical and physical in-use stability has been demonstrated for 4 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store and transport frozen (-20 °C ±5 °C).

Do not refreeze after thawing.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I plus glass vial with a butyl rubber stopper and an aluminium/plastic flip-off seal, containing 1 mL concentrate.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

General precautions
Procedures for proper handling, including personal protective equipment (e.g. gloves), and disposal of anticancer medicines should be followed.
The solution for infusion should be prepared by a healthcare professional using proper aseptic technique throughout the handling of this medicinal product.

Preparation and administration

Preparing the infusion
Ensure the following components required for dose preparation and administration are available prior to thawing ELZONRIS:

- One infusion syringe pump
- One empty 10 mL sterile vial
- Sodium chloride 9 mg/mL (0.9%) solution for injection
- Three 10 mL sterile syringes
- One 1 mL sterile syringe
- One mini-bifuse Y-connector
- Microbore tubing
- One 0.2 µm low protein binding polyethersulfone in-line filter

Use only if the solution is clear and colourless or with a few white to translucent particles.
Allow vials to thaw at 25 °C or below for up to 1 hour in the outer carton. Do not refreeze a vial once thawed.

Determining dosage amount
Calculation to determine the total ELZONRIS dose (mL) to be administered (see section 4.2):

$$\frac{\text{ELZONRIS dose (mcg/kg) x patient's body weight (kg)}}{\text{Diluted vial concentration (100 mcg/ml)}} = \text{Total dose (mL) to be administered}$$

A 2-step process is required for preparation of the final ELZONRIS dose:

Step 1 -prepare 10 mL of 100 mcg/mL ELZONRIS
- Using a sterile 10 mL syringe, transfer 9 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to an empty sterile 10 mL vial.
- Gently swirl the ELZONRIS vial to mix the contents, remove the cap, and using a sterile 1 mL syringe, withdraw 1 mL of thawed ELZONRIS from the product vial.

- Transfer the 1 mL of ELZONRIS into the 10 mL vial containing the 9 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Gently invert the vial at least 3 times to mix the contents. Do not shake vigorously.
- Following dilution the final concentration of ELZONRIS is 100 mcg/mL.

Step 2 – Prepare the ELZONRIS infusion set.

- Calculate the required volume of diluted ELZONRIS (100 mcg/mL) according to patient's weight.
- Draw up the required volume into a new syringe (if more than 10 mL of diluted ELZONRIS (100 mcg/mL) is required for the calculated patient dose, repeat step 1 with a second vial of ELZONRIS). Label the ELZONRIS syringe.
- Prepare a separate syringe with at least 3 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to be used to flush the administration set once the ELZONRIS dose is delivered.
- Label the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe.
- Connect the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe to one arm of the Y-connector and ensure the clamp is closed.
- Connect the product syringe to the other arm of the Y-connector and ensure the clamp is closed.
- Connect the terminal end of the Y-connector to the microbore tubing.
- Remove the cap from the supply side of the 0.2 µm filter and attach it to the terminal end of the microbore tubing.
- Unclamp the arm of the Y-connector connected to the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe. Prime the Y-connector up to the intersection (do not prime the full infusion set with sodium chloride 9 mg/mL (0.9%) solution for injection). Re-clamp the Y-connector line on the sodium chloride 9 mg/mL (0.9%) solution for injection flush arm.
- Remove the cap on the terminal end of the 0.2 µm filter and set it aside. Unclamp the arm of the Y-connector connected to the product syringe, and prime the entire infusion set, including the filter. Recap the filter, and re-clamp the Y-connector line on the product side. The infusion set is now ready for delivery for dose administration.

The diluted solution should be used immediately once prepared.

Administration

1. Establish venous access and maintain with sterile sodium chloride 9 mg/mL (0.9%) solution for injection.
2. Administer the prepared ELZONRIS dose via infusion with an infusion syringe pump over 15 minutes. The total infusion time will be controlled using an infusion syringe pump to deliver the entire dose and the sodium chloride 9 mg/mL (0.9%) solution for injection flush over 15 minutes.
3. Insert the ELZONRIS syringe into the infusion syringe pump, open the clamp on the ELZONRIS side of the Y-connector and deliver the prepared ELZONRIS dose.
4. Once the ELZONRIS syringe has been emptied, remove it from the pump and place the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe in the infusion syringe pump.
5. Open the clamp on the sodium chloride 9 mg/mL (0.9%) solution for injection flush side of the Y-connector and resume infusion via the infusion syringe pump at the pre-specified flow to push the remaining ELZONRIS dose out of the infusion line to complete delivery.

Disposal

ELZONRIS is for single use only.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Stemline Therapeutics B.V.
Basisweg 10,
1043 AP Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1504/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 January 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

FUJIFILM Diosynth Biotechnologies U.S.A., Inc
6051 George Watts Hill Drive
Research Triangle Park
NC 27709
USA

Name and address of the manufacturer(s) responsible for batch release

Stemline Therapeutics B.V.
Basisweg 10,
1043 AP Amsterdam
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of ELZONRIS in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication

media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at healthcare professionals to enhance their awareness of the early signs and symptoms of specific adverse reactions associated with capillary leak syndrome (CLS).

The MAH shall ensure that in each Member State where ELZONRIS is marketed, all healthcare professionals who are expected to use ELZONRIS are provided with the following educational package:

- Guide for healthcare professionals
- Patient alert card

- **Guide for healthcare professionals**:
  - Description of CLS which can occur with ELZONRIS
  - Before initiating ELZONRIS therapy check cardiac function and serum albumin
  - During treatment monitor serum albumin, weight gain, new onset or worsening oedema, including pulmonary oedema and hypotension including haemodynamic instability
  - Inform the patient about the risk of CLS and how to recognise CLS symptoms
  - Provide patients with the patient alert card

- **Patient alert card:**
  - That ELZONRIS treatment may increase the potential risk of CLS
  - Signs or symptoms of CLS
  - Patients experiencing or suspecting CLS should immediately contact their prescriber
  - Contact details of the ELZONRIS prescriber

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to collect further safety and efficacy data for ELZONRIS, the MAH should submit the results of a study based on a registry in patients with Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) according to an agreed protocol.	Reports to be submitted as part of the annual re-assessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ELZONRIS 1 mg/mL concentrate for solution for infusion
tagraxofusp

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 mg of tagraxofusp in 1 mL of concentrate.

3. LIST OF EXCIPIENTS

Trometamol, sodium chloride, sorbitol (E420), water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 mg/mL

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen
Keep the vial in the outer carton in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Stemline Therapeutics B.V.
Basisweg 10,
1043 AP Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/20/1504/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ELZONRIS 1 mg/mL sterile concentrate
tagraxofusp
IV after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg/mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ELZONRIS 1 mg/mL concentrate for solution for infusion
tagraxofusp

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ELZONRIS is and what it is used for

ELZONRIS contains the active substance tagraxofusp. Tagraxofusp, an anti-cancer medicine, is made from two proteins from different sources. One of the proteins can kill cancer cells. This protein is delivered to the cancer cell by the second protein.

ELZONRIS is used to treat adult patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN).

BPDCN is a cancer of a rare type of immature immune cells called ‘plasmacytoid dendritic cells’. It can affect many organs including the skin, bone marrow, and lymph nodes.

2. What you need to know before you are given ELZONRIS

Do not use ELZONRIS
- if you are allergic to tagraxofusp or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before using ELZONRIS and during treatment if you:

- suddenly gain weight after starting treatment, have new or worsening swelling of your face, limbs or joints (oedema) or dizziness (a symptom of low blood pressure). These may be signs of a potentially life-threatening condition known as capillary leak syndrome. For more information see “Capillary Leak Syndrome” in section 4.
- get a whistling sound during breathing (wheezing) or have difficulty breathing, hives/ rash, itching, or swelling (signs of an allergic reaction).
- have been told you have a low level of platelets in your blood (thrombocytopenia).
- have been told you have a low level of a type of white blood cell called a neutrophil (neutropenia).

- have dizziness, decreased urination, confusion, vomiting, nausea, swelling, shortness of breath, or changes in heart rhythm (signs of tumour lysis syndrome).
- have abnormal liver test results (possible sign of serious liver injury).
- have hereditary fructose intolerance (HFI), a rare genetic disorder which means you can't break down sugar in foods and drinks.
- have kidney or liver problems.
- start getting headaches, or feeling confused or drowsy, or having speech, vision or memory problems.
- have been told you have cancer in your central nervous system (CNS). You may be given a different medicine to treat this.

Your doctor will monitor you and perform regular blood tests to make sure that it is safe for you to use this medicine. If you have any problems, your treatment may be temporarily stopped and started again when you feel better.

Children and adolescents
ELZONRIS is not recommended for anyone under the age of 18 years. This is because there is limited information on how well it works in this age group.

Other medicines and ELZONRIS
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

You should not use this medicine if you are pregnant unless you and your doctor decide that the benefit to you outweighs the potential risk to the unborn baby .

You should not breast-feed during treatment with ELZONRIS and for at least 1 week after your last dose. It is not known if ELZONRIS passes into breast-milk.

If you are a woman who can become pregnant, you will have a pregnancy test about a week before starting treatment with ELZONRIS.

You should continue to take your contraception for at least 1 week after your last dose of ELZONRIS. Talk to your doctor about the best contraception for you and before stopping your contraception.

Driving and using machines
Tagraxofusp is unlikely to affect your ability to drive or use machines.

ELZONRIS contains sorbitol (E420) and sodium
Sorbitol is a source of fructose. If you have hereditary fructose intolerance (HFI), a rare genetic disorder, you must not receive this medicine. Patients with HFI cannot break down fructose, which may cause serious side effects.

You must tell your doctor before receiving this medicine if you have HFI or if you can no longer take sweet foods or drinks because you feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea.

This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

3. How ELZONRIS is given

ELZONRIS will be given to you in a hospital or clinic under the supervision of a doctor.

About an hour before your treatment begins, you will be given medicines to help prevent an allergic reaction, including anti-histamines, a corticosteroid and paracetamol.

The amount of ELZONRIS given to you is based on your body weight and will be calculated by your doctor. The daily recommended dose is 12 micrograms per kilogram of your body weight. It is given as a 15-minute drip into a vein (intravenous infusion), once a day, for the first 5 days of a 21-day cycle.

The first cycle will be given to you in hospital. You will be monitored for any side effectsduring treatment and for at least 24 hours after the last dose.

You will usually have more than one cycle of treatment. Your doctor will decide how many treatments you will receive.

If the first cycle does not cause troublesome side effects, your next cycle of treatment may be given in a clinic. You will be monitored during treatment.

If you miss a dose of ELZONRIS
It is very important for you to keep all your appointments to receive ELZONRIS. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using ELZONRIS
Do not stop treatment with ELZONRIS without first talking to your doctor. Stopping your treatment may make your condition worse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects:
Tell your doctor **immediately** if you experience the following side effects, as you may need urgent medical attention:

- any one or combination of: weight gain, swelling or puffiness, which may be associated with passing water less frequently, difficulty breathing, abdominal swelling and feeling of fullness, and a general feeling of tiredness. These symptoms generally develop in a rapid fashion. These could be symptoms of a condition called “capillary leak syndrome” which causes blood to leak from the small blood vessels into your body and needs urgent medical attention.

Other side effects:
Tell your doctor if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):
- Abnormal blood tests (decreased platelets [thrombocytopenia]; red blood cells [anaemia]; decreased albumin in the blood [hypoalbuminemia])
- Low blood pressure (hypotension)
- Feeling or being sick (nausea; vomiting)
- Fever (pyrexia)
- Chills
- Tiredness (fatigue)
- Swelling of limbs and/or joints (peripheral oedema)
- Abnormal liver function tests (increased aspartate aminotransferase; increased alanine aminotransferase)

- Weight gain

Common (may affect up to 1 in 10 people):
- Skin infection (cellulitis)
- Decreased white blood cells with/without a fever (neutropenia, leukopenia, lymphopenia; febrile neutropenia)
- Complications from breakdown of cancer cells (tumour lysis syndrome)
- Reaction to treatment [including fever, feeling sick, headache, rash, rapid heartbeat] (cytokine release syndrome)
- Abnormal blood tests [Increased white blood cells (leukocytosis), increased uric acid in the blood (hyperuricaemia); decreased calcium in the blood (hypocalcaemia); decreased magnesium in the blood (hypomagnesaemia); decreased sodium in the blood (hyponatraemia); decreased potassium in the blood (hypokalaemia), increased blood potassium (hyperkalaemia), increased blood phosphate (hyperphosphataemia), increased bile pigment in the blood (hyperbilirubinemia), increased level of blood sugar (hyperglycaemia), incresed time for blood to clot (activated partial thromboplastin time prolonged, international normalised ratio increased)]
- Decreased appetite
- Feeling confused
- Fainting (syncope)
- Headache
- Dizziness
- Blurred vision
- Fluid around the heart (percardial effusion)
- Abnormal or fast heartbeat (tachycardia, sinus tachycardia)
- Blushing (flushing)
- Decreased level of oxygen in the body (hypoxia)
- Fluid in the lungs (pulmonary oedema)
- Build-up of fluid around the lungs that may cause breathlessness (pleural effusion)
- Difficulty breathing (dyspnoea)
- Nose bleeds (epistaxis)
- Coughing
- Difficulty swallowing (dysphagia)
- Diarrhoea
- Constipation
- Dry mouth or a swollen and sore mouth (stomatitis)
- Indigestion (dyspepsia)
- Itchy skin (pruritis)
- Skin rashes
- Excessive sweating (hyperhydrosis)
- Very small purple, red, or brown spots on the skin (petechiae)
- Pain in shoulders, neck, wrists, legs, and/or arms (pain in extremity), chest, back, joints (arthralgia), muscles (myalgia) or bones.
- Muscle weakness
- Kidneys suddenly stop working (acute kidney injury) and/or abnormal kidney function tests (increased blood creatinine)
- Flu-like symptoms such as aches and pains, fever and shaking
- Chest pain
- Generally feeling unwell (malaise)
- Abnormal heart rhythm (Electrocardiogram QT prolonged)
- Increased levels of enzymes in the blood seen in blood tests (lactate dehydrogenase, alkaline phosphatase and creatine phosphokinase)
- Flushing, shivering, fits, fever, trouble breathing, low blood pressure, rapid heartbeat, sudden swelling of your face, tongue, or trouble swallowing during the infusion or after the infusion on the first day of treatment (infusion-related reaction)
- Bruising (contusions)

Uncommon: may affect up to 1 in 100 people:
- Lung infection (pneumonia)
- Urinary tract infection
- Gum disease (gingivitis) including bleeding gums
- Blood test abnormalities [decreased phosphate in the blood (hypophosphataemia), increased lactic acid in the bloodstream (lactic acidosis/acidosis), decreased levels of a blood clotting protein (blood fibrinogen decreased)]
- Unusual mood changes including depression and anxiety
- Trouble sleeping (insomnia)
- Brain function disturbances (encephalopathy/ metabolic encephalopathy)
- Stroke
- Loss of movement in face (facial paralysis)
- Persistent bad taste in mouth (dysgeusia)
- Worsening of multiple sclerosis (relapse)
- Drowsiness (somnolence)
- Tingling or numbness (paraesthesia, peripheral sensory neuropathy)
- Weakness in muscles (peripheral motor neuropathy)
- Bleeding in the white of the eye (conjunctival haemorrhage)
- Eye redness (ocular hyperaemia)
- Eye floaters (vitreous floaters)
- Irregular heartbeat which can lead to the heart stopping (supraventricular extrasystoles, ventricular fibrillation, atrial fibrillation)
- Slow heart rate (bradycardia)
- Heart attack (myocardial infarction)
- High blood pressure (hypertension)
- Lungs do not function as they should, causing breathlessness (respiratory failure)
- Noisy breathing (wheezing)
- Mouth and/or throat pain (oropharyngeal pain)
- Rapid breathing (tachypnoea)
- Bloated stomach and stomach ache
- Blisters on the tongue
- Blood blister on tongue (tongue haematoma)
- Swelling of the face, tongue, limbs or joints (angioedema)
- Redness, swelling and pain on the palms of the hands and/or the soles of the feet (palmar-plantar erythrodysesthesia syndrome)
- Hives (urticaria)
- Hair loss (alopecia)
- Skin pain
- Dry, red, itchy skin and/or sores on the lower legs (stasis dermatitis)
- Cold sweat
- Dry skin
- Pain of joints, muscles and/or bones, including tail bone (musculoskeletal pain, coccydynia)
- Muscle spasm
- Muscle pain, weakness, dark or brown urine (rhabdomyolysis)
- Kidney failure
- Difficulty passing urine
- Pain in lower back/ abdomen and/or painful urination (urinary tract pain)
- Frequent daytime urination (pollakiuria)
- Urine test abnormality [increased protein (proteinuria)]
- Inability to tolerate side effects of this medicine (drug intolerance)
- Low body temperature (hypothermia)
- Fever or low body temperature, increased heart rate, increased breathing (systemic inflammatory response syndrome)
- Increase in time taken for blood to clot (shown in blood tests)
- Test positive for bacteria
- Decreased weight

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ELZONRIS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial and carton after EXP. The expiry date refers to the last day of that month.

Unopened vial: Store and transport frozen (-20 °C±5 °C)

Keep the vial in the outer carton in order to protect from light.

Diluted solution: use immediately or store below 25 °C and use within 4 hours. Do not re-freeze, once thawed.

Do not throw away any medicines via wastewater or household waste. Your healthcare professional will throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ELZONRIS contains
- The active substance is tagraxofusp. Each vial contains 1 mg of tagraxofusp in 1mL of concetrate.
- The other ingredients are trometamol, sodium chloride, sorbitol (E420) and water for injections (see section 2 'ELZONRIS contains sorbitol (E420) and sodium').

What ELZONRIS looks like and contents of the pack
ELZONRIS concentrate for solution for infusion (sterile concentrate) is a clear, colourless liquid. A few white to translucent particles may be present.

The pack size is 1 glass vial per carton.

Marketing Authorisation Holder
Stemline Therapeutics B.V.
Basisweg 10,
1043 AP Amsterdam
Netherlands

Manufacturer
Stemline Therapeutics B.V.
Basisweg 10,
1043 AP Amsterdam
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

The following information is intended for healthcare professionals only:

General precautions
Procedures for proper handling, including personal protective equipment (e.g. gloves), and disposal of anticancer medicines should be followed.
The solution for infusion should be prepared by a healthcare professional using proper aseptic technique throughout the handling of this medicinal product.

Preparation and administration

Preparing the infusion
Ensure the following components required for dose preparation and administration are available prior to thawing ELZONRIS:

- One infusion syringe pump
- One empty 10 mL sterile vial

- Sodium chloride 9 mg/mL (0.9%) solution for injection
- Three 10 mL sterile syringes
- One 1 mL sterile syringe
- One mini-bifuse Y-connector
- Microbore tubing
- One 0.2 µm polyethersulfone in-line low protein-binding filter

Use only if the solution is clear and colourless or with a few white to translucent particles.
Allow vials to thaw at 25 °C or below for up to 1 hour in the outer carton. Do not refreeze a vial once thawed.

Determining dosage amount
Calculation to determine the total ELZONRIS dose (mL) to be administered (see Summary of Product Characteristics, section 4.2):

$$\frac{\text{ELZONRIS dose (mcg/kg) x patient's body weight (kg)}}{\text{Diluted vial concentration (100 mcg/ml)}} = \text{Total dose (mL) to be administered}$$

A 2-step process is required for preparation of the final ELZONRIS dose:

Step 1 -prepare 10 mL of 100 mcg/mL ELZONRIS
- Using a sterile 10 mL syringe, transfer 9 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to an empty sterile 10 mL vial.
- Gently swirl the ELZONRIS vial to mix the contents, remove the cap, and using a sterile 1 mL syringe, withdraw 1 mL of thawed ELZONRIS from the product vial.
- Transfer the 1 mL of ELZONRIS into the 10 mL vial containing the 9 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Gently invert the vial at least 3 times to mix the contents. Do not shake vigorously.
- Following dilution the final concentration of ELZONRIS is 100 mcg/mL.

Step 2 – Prepare the ELZONRIS infusion set.
- Calculate the required volume of diluted ELZONRIS (100 mcg/mL) according to patient's weight.
- Draw up the required volume into a new syringe (if more than 10 mL of diluted ELZONRIS (100 mcg/mL) is required for the calculated patient dose, repeat step 1 with a second vial of ELZONRIS). Label the ELZONRIS syringe.
- Prepare a separate syringe with at least 3 mL of sodium chloride 9 mg/mL (0.9%) solution for injection to be used to flush the administration set once the ELZONRIS dose is delivered.
- Label the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe.
- Connect the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe to one arm of the Y-connector and ensure the clamp is closed.
- Connect the product syringe to the other arm of the Y-connector and ensure the clamp is closed.
- Connect the terminal end of the Y-connector to the microbore tubing.
- Remove the cap from the supply side of the 0.2 µm filter and attach it to the terminal end of the microbore tubing.
- Unclamp the arm of the Y-connector connected to the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe. Prime the Y-connector up to the intersection (do not prime the full infusion set with sodium chloride 9 mg/mL (0.9%) solution for injection). Re-clamp the Y-connector line on the sodium chloride 9 mg/mL (0.9%) solution for injection flush arm.
- Remove the cap on the terminal end of the 0.2 µm filter and set it aside. Unclamp the arm of the Y-connector connected to the product syringe, and prime the entire infusion set, including the filter. Recap the filter, and re-clamp the Y-connector line on the product side. The infusion set is now ready for delivery for dose administration.

The diluted solution should be used immediately once prepared.

Administration

1. Establish venous access and maintain with sterile sodium chloride 9 mg/mL (0.9%) solution for injection.
2. Administer the prepared ELZONRIS dose via infusion with an infusion syringe pump over 15 minutes. The total infusion time will be controlled using an infusion syringe pump to deliver the entire dose and the sodium chloride 9 mg/mL (0.9%) solution for injection flush over 15 minutes.
3. Insert the ELZONRIS syringe into the infusion syringe pump, open the clamp on the ELZONRIS side of the Y-connector and deliver the prepared ELZONRIS dose.
4. Once the ELZONRIS syringe has been emptied, remove it from the pump and place the sodium chloride 9 mg/mL (0.9%) solution for injection flush syringe in the infusion syringe pump.
5. Open the clamp on the sodium chloride 9 mg/mL (0.9%) solution for injection flush side of the Y-connector and resume infusion via the infusion syringe pump at the pre-specified flow to push the remaining ELZONRIS dose out of the infusion line to complete delivery.