Capillary Leak Syndrome (CLS)

Management Guidelines

INDICATION

- ELZONRIS is a CD123-directed cytotoxin indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older

Boxed WARNING: CAPILLARY LEAK SYNDROME

- **Capillary Leak Syndrome (CLS) which may be life-threatening or fatal, can occur in patients receiving ELZONRIS. Monitor for signs and symptoms of CLS and take actions as recommended.**

This information is for informational and educational purposes only and is not a substitute for the professional judgment of a healthcare professional.

Please see Important Safety Information on slides 15-17, and full Prescribing Information, including Boxed WARNING, at ELZONRIS.com/hcp.

Reference: ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022.

ELZONRIS® (tagraxofusp-erzs) Injection

ELZONRIS® (tagraxofusp-erzs)

ELZONRIS is a CD123-directed cytotoxin indicated for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.

Boxed WARNING: CAPILLARY LEAK SYNDROME

Capillary Leak Syndrome (CLS) which may be life-threatening or fatal, can occur in patients receiving ELZONRIS. Monitor for signs and symptoms of CLS and take actions as recommended.

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Summary of CLS Events With ELZONRIS® (tagraxofusp-erzs)

CLS, which may be life-threatening or fatal, can occur in patients receiving ELZONRIS. Monitor for signs and symptoms of CLS and take actions as recommended

- In patients receiving ELZONRIS 12 mcg/kg (N=122) in clinical trials, the overall incidence of CLS was 53% (n=65), including:
  - Grade 1 or 2 in 43% (n=52)
  - Grade 3 in 7% (n=8)
  - Grade 4 in 1% (n=1)
  - Grade 5 in 3% (n=4)

The median time to onset was 4 days (range - 1 to 46 days), and all but 5 patients experienced an event in Cycle 1.

Common Terminology Criteria for Adverse Events: Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death.

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Common Signs and Symptoms of CLS

- Common signs and symptoms associated with CLS that were reported during treatment with ELZONRIS included:
  - Hypoalbuminemia
  - Edema, including pulmonary edema
  - Weight gain
  - Hypotension
  - Hemodynamic instability

Reference: ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022.

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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** (q12h or more frequently as practical) until serum albumin is ≥**3.5 g/dL** AND not more than **0.5 g/dL lower** than the value measured prior to dosing initiation of the current cycle	**Interrupt ELZONRIS dosing until the relevant CLS sign/symptom has resolved**[1]
	Serum albumin reduced by **≥0.5 g/dL** from the albumin value measured prior to ELZONRIS dosing initiation of the current cycle		
	A predose body weight that is increased **by ≥1.5 kg** over the previous day's predose weight	Administer **25 g intravenous albumin** (q12h or more frequently as practical) and manage fluid status as indicated clinically (eg, generally with intravenous fluids and vasopressors if hypotensive and with diuretics if normotensive or hypertensive) **until body weight increase has resolved** (ie, the increase is no longer ≥**1.5 kg** greater than the previous day's predose weight)	
	Edema, fluid overload, and/or hypotension	Administer **25 g intravenous albumin** (q12h 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 hemodynamic instability
- ELZONRIS administration should be held for the remainder of the cycle if CLS signs/symptoms have not resolved or the patient required measures to treat hemodynamic instability (eg, required administration of intravenous fluids and/or vasopressors to treat hypotension) (even if resolved), and
- ELZONRIS administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is hemodynamically stable.

Reference: ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022.

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CLS Risk Management Strategy[1]

PREPARING FOR ELZONRIS ADMINISTRATION

When Considering to Initiate ELZONRIS

- Ensure that the patient has adequate cardiac function* and serum albumin is ≥ 3.2 g/dL

Prior to the First Dose of the First Cycle

- Ensure serum albumin is ≥ 3.2 g/dL before administering ELZONRIS
- Weigh patient to establish baseline weight for subsequent dose

* In clinical studies, patients had a normal left ventricular ejection fraction ≥ institutional lower limit of normal as measured by multigated acquisition scan or 2-dimensional echocardiography within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram.[2]

Please refer to the ELZONRIS full prescribing information for full dosing and administration information.

DURING ELZONRIS ADMINISTRATION

During treatment, assess patients for common signs/symptoms of CLS **before each dose is given**:

- Hypoalbuminemia
  - Ensure serum albumin is ≥ 3.5 g/dL and not reduced by ≥ 0.5 g/dL from the albumin value measured prior to ELZONRIS dosing initiation of the current cycle
- Weight gain
  - Ensure predose body weight is not increased by ≥ 1.5 kg over pretreatment weight on the previous treatment day
- New onset or worsening edema, including pulmonary edema
- Hypotension
  - Ensure systolic blood pressure > 80 mmHg

Reference: 1. ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022. **2.** Data on File.

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CLS Risk Management Strategy (cont'd)

ELZONRIS infusion should be withheld for common signs/symptoms of CLS, including:

- **Hypoalbuminemia** (albumin reduced to < 3.5 g/dL or by ≥ 0.5 g/dL below the level at the start of the cycle)
- **Weight gain** (body weight increased by ≥ 1.5 kg over pretreatment weight on the previous treatment day)
- New-onset or worsening **edema**, including pulmonary edema
- **Hypotension** (systolic blood pressure ≤ 80 mmHg) or hemodynamic instability

Reference: ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022.

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Supportive Care: Recommended Actions

HYPOALBUMINEMIA	WEIGHT GAIN	EDEMA, FLUID, OVERLOAD, AND/OR HYPOTENSION
Administer **25 g IV albumin** (q12h or more frequently as practical) until serum albumin is ≥ 3.5 g/dL AND not more than 0.5 g/dL lower than the value measured prior to dosing initiation of the current cycle.	Administer **25 g IV albumin** (q12h or more frequently as practical) until body weight increase has resolved. Manage fluid status as indicated clinically (eg, generally with **IV fluids** and **vasopressors** if hypotensive and with **diuretics** if normotensive or hypertensive), until body weight increase has resolved.	Administer **25 g IV albumin** (q12h 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 **IV fluids and/or diuretics** or other blood pressure management, until resolution of CLS sign/symptom or as clinically indicated.

Reference: ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022.

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CLS Risk Management Strategy (cont'd)

ELZONRIS administration may **resume in the same cycle** (up to Day 10 of the cycle) if all CLS signs/symptoms have resolved and the patient did not require measures to treat hemodynamic instability (eg, required administration of intravenous fluids and/or vasopressors to treat hypotension).

ELZONRIS administration should be **held for the remainder of the cycle** if CLS signs/symptoms have not resolved or the patient required measures to treat hemodynamic instability (eg, required administration of intravenous fluids and/or vasopressors to treat hypotension) (even if resolved).

ELZONRIS administration may **only resume in the next cycle** if all CLS signs/symptoms have resolved and the patient is hemodynamically stable.

Reference: ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022.

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Patient Observation

- Cycle 1
  - The first cycle must be administered in the inpatient setting
  - Observe patients for at least 24 hours after the last infusion of the first cycle
- Subsequent cycles
  - Subsequent cycles may be administered in an inpatient setting or an appropriate outpatient setting
  - Observe patients for a minimum of 4 hours following each infusion

Reference: ELZONRIS [prescribing information]. New York, NY, US: Stemline Therapeutics, Inc.; November 2022.

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Counsel Patients Upon Discharge

- Advise patients of the risk of CLS, and to contact their healthcare professional for signs and symptoms associated with CLS, including:
  - New or worsening edema
  - Weight gain
  - Shortness of breath and/or
  - Low blood pressure after infusion
- Advise patients to weigh themselves daily

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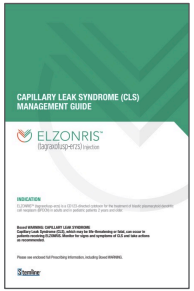
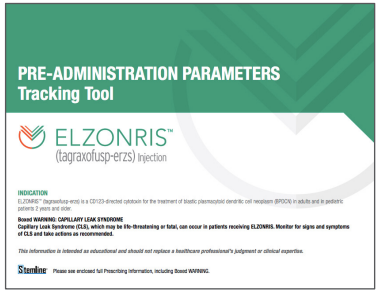
ELZONRIS Resources

For HCPs:

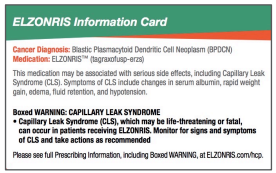


CLS Management Guide



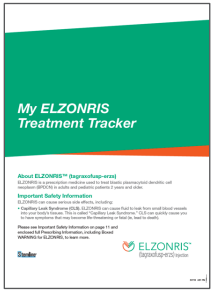
Pre-Administration Parameters Tracking Tool

For patients:



Patient Information Card

ELZONRIS Treatment Guide



Treatment Tracker

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Summary

- CLS is a serious side effect of ELZONRIS and can be life-threatening or fatal if not properly managed
- Common signs and symptoms associated with CLS that were reported during treatment with ELZONRIS included:
  - Hypoalbuminemia
  - Edema, including pulmonary edema
  - Weight gain
  - Hypotension
  - Hemodynamic instability

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Summary (cont'd)

CLS risk-managing strategies

- Vigilant monitoring of CLS signs/symptoms
  - Daily labs
  - Albumin levels
  - Body weight
- Stop ELZONRIS dosing in patients who present with CLS signs/symptoms
- Administer albumin and aggressively manage fluid status
- Consider additional interventions
- Follow ELZONRIS dose management guidelines once CLS signs and symptoms have resolved:
  - Allow dose delays up to day 10 of each cycle

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Important Safety Information

Boxed WARNING: CAPILLARY LEAK SYNDROME

- **Capillary Leak Syndrome (CLS) which may be life-threatening or fatal, can occur in patients receiving ELZONRIS. Monitor for signs and symptoms of CLS and take actions as recommended**

WARNINGS AND PRECAUTIONS

Capillary Leak Syndrome

- Capillary leak syndrome (CLS), including life-threatening and fatal cases, has been reported among patients treated with ELZONRIS. In patients receiving ELZONRIS in clinical trials, the overall incidence of CLS was 53% (65/122), including Grade 1 or 2 in 43% (52/122) of patients, Grade 3 in 7% (8/122) of patients, Grade 4 in 1% (1/122) of patients, and four fatalities (3%). The median time to onset was 4 days (range - 1 to 46 days), and all but 5 patients experienced an event in Cycle 1.
- Before initiating therapy with ELZONRIS, ensure that the patient has adequate cardiac function and serum albumin is greater than or equal to 3.2 g/dL. During treatment with ELZONRIS, monitor serum albumin levels prior to the initiation of each dose of ELZONRIS and as indicated clinically thereafter, and assess patients for other signs or symptoms of CLS, including weight gain, new onset or worsening edema, including pulmonary edema, hypotension or hemodynamic instability.

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Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hypersensitivity Reactions

- ELZONRIS can cause severe hypersensitivity reactions. In patients receiving ELZONRIS in clinical trials, hypersensitivity reactions were reported in 43% (53/122) of patients treated with ELZONRIS and were Grade ≥ 3 in 7% (9/122). Manifestations of hypersensitivity reported in ≥ 5% of patients include rash, pruritus, and stomatitis. Monitor patients for hypersensitivity reactions during treatment with ELZONRIS. Interrupt ELZONRIS infusion and provide supportive care as needed if a hypersensitivity reaction should occur.

Hepatotoxicity

- Treatment with ELZONRIS was associated with elevations in liver enzymes. In patients receiving ELZONRIS in clinical trials, elevations in ALT occurred in 79% (96/122) and elevations in AST occurred in 76% (93/122). Grade 3 ALT elevations were reported in 26% (32/122) of patients. Grade 3 AST elevations were reported in 30% (36/122) and Grade 4 AST elevations were reported in 3% (4/122) of patients. Elevated liver enzymes occurred in the majority of patients in Cycle 1 and were reversible following dose interruption.

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Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Hepatotoxicity (cont'd)

- Monitor alanine aminotransferase (ALT) and aspartate aminotransferase (AST) prior to each infusion with ELZONRIS. Withhold ELZONRIS temporarily if the transaminases rise to greater than 5 times the upper limit of normal and resume treatment upon normalization or when resolved.

ADVERSE REACTIONS:

Most common adverse reactions (incidence ≥ 30%) are capillary leak syndrome, nausea, fatigue, pyrexia, peripheral edema, and weight increase. Most common laboratory abnormalities (incidence ≥ 50%) are decreases in albumin, platelets, hemoglobin, calcium, and sodium, and increases in glucose, ALT and AST.

Please see full Prescribing Information, including Boxed WARNING.

To report SUSPECTED ADVERSE REACTIONS, contact Stemline Therapeutics, Inc. at 1-877-332-7961 or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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