Capillary Leak Syndrome (CLS)

Management Guidelines

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

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

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

Please see full Prescribing Information, including Boxed WARNING, available at ELZONRIS.com/hcp.
ELZONRIS® (tagraxofusp-erzs)

ELZONRIS is a CD123-directed cytotoxin 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.
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=94) in clinical trials, the overall incidence of CLS was 55% (n=52), including:
  - Grade 1 or 2 in 46% (n=43)
  - Grade 3 in 6% (n=6)
  - Grade 4 in 1% (n=1)
  - Grade 5 in 2% (n=2)

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

- Common signs and symptoms (incidence ≥ 20%) associated with CLS that were reported during treatment with ELZONRIS included:
  - Hypoalbuminemia
  - Edema
  - Weight gain
  - Hypotension
### CLS Management Guidelines

<table>
<thead>
<tr>
<th>TIME OF PRESENTATION</th>
<th>CLS SIGN/SYMPOTOM</th>
<th>RECOMMENDED ACTION</th>
<th>ELZONRIS DOSING MANAGEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to first dose of ELZONRIS in cycle 1</td>
<td>Serum albumin &lt; 3.2 g/dL</td>
<td>Administer ELZONRIS when serum albumin ≥ 3.2 g/dL</td>
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<tr>
<td>During ELZONRIS dosing</td>
<td>Serum albumin reduced by ≥ 0.5 g/dL from the albumin value measured prior to ELZONRIS dosing initiation of the current cycle</td>
<td>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</td>
<td>Interrupt ELZONRIS dosing until the relevant CLS sign/symptom has resolveda</td>
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<tr>
<td></td>
<td>A predose body weight that is increased by ≥ 1.5 kg over the previous day’s predose weight</td>
<td>Administer 25 g intravenous albumin (q12h 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 predose weight)</td>
<td></td>
</tr>
</tbody>
</table>
| | 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 | |

*aELZONRIS 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 (e.g., 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.*
CLS Risk Management Strategy

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

*D 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.

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
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
## Supportive Care: Recommended Actions

<table>
<thead>
<tr>
<th>HYPOALBUMINEMIA</th>
<th>WEIGHT GAIN</th>
<th>EDEMA, FLUID, OVERLOAD, AND/OR HYPOTENSION</th>
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<tr>
<td>Administer <strong>25 g IV albumin</strong> (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.</td>
<td>Administer <strong>25 g IV albumin</strong> (q12h or more frequently as practical) until body weight increase has resolved. Manage fluid status as indicated clinically (e.g., generally with <strong>IV fluids</strong> and <strong>vasopressors</strong> if hypotensive and with <strong>diuretics</strong> if normotensive or hypertensive), until body weight increase has resolved.</td>
<td>Administer <strong>25 g IV albumin</strong> (q12h or more frequently as practical) until serum albumin is ≥ 3.5 g/dL. Administer <strong>1 mg/kg of methylprednisolone</strong> (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 <strong>IV fluids and/or diuretics</strong> or other blood pressure management, until resolution of CLS sign/symptom or as clinically indicated.</td>
</tr>
</tbody>
</table>
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 (e.g., 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 (e.g., 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.
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

Please see full Prescribing Information, including Boxed WARNING, available at ELZONRIS.com/hcp.
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
For HCPs:

- CLS Management Guide
- Pre-Administration Parameters Tracking Tool

For patients:

- Patient Information Card
- ELZONRIS Treatment Guide
- Treatment Tracker

Please see full Prescribing Information, including Boxed WARNING, available at ELZONRIS.com/hcp.
Summary

- CLS is a serious side effect of ELZONRIS and can be life-threatening or fatal if not properly managed.

- Common signs and symptoms (incidence ≥ 20%) associated with CLS that were reported during treatment with ELZONRIS included:
  - Hypoalbuminemia
  - Edema
  - Weight gain
  - Hypotension
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
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

- ELZONRIS can cause capillary leak syndrome (CLS), which may be life-threatening or fatal if not properly managed. The overall incidence of CLS in clinical trials was 55% in patients receiving ELZONRIS, including 46% in Grades 1 or 2, 6% in Grade 3, 1% in Grade 4, and 2 fatal events. Common signs and symptoms (incidence ≥ 20%) associated with CLS that were reported during treatment with ELZONRIS include hypoalbuminemia, edema, weight gain, and hypotension.

- Before initiating therapy with ELZONRIS, ensure that the patient has adequate cardiac function and serum albumin is ≥ 3.2 g/dL.
 WARNINGS AND PRECAUTIONS (cont’d)

Capillary Leak Syndrome (cont’d)

• During treatment with ELZONRIS, ensure that serum albumin levels are ≥ 3.5 g/dL and have not been reduced by ≥ 0.5 g/dL from the albumin value measured prior to dosing initiation of the current cycle. Monitor serum albumin levels prior to the initiation of each dose or more often as indicated clinically thereafter. Additionally, assess patients for other signs or symptoms of CLS, including weight gain, new onset or worsening edema including pulmonary edema, hypotension, or hemodynamic instability

• Counsel patients to seek immediate medical attention should signs or symptoms of CLS occur at any time

Hypersensitivity Reactions

• ELZONRIS can cause severe hypersensitivity reactions. Grade 3 or higher events were reported in 10% of patients in clinical trials. Monitor patients for hypersensitivity reactions during treatment with ELZONRIS. Interrupt ELZONRIS infusion and provide supportive care as needed if a hypersensitivity reaction should occur. If the reaction is severe, discontinue ELZONRIS permanently
Important Safety Information (cont’d)

WARNINGS AND PRECAUTIONS (cont’d)

Hepatotoxicity

• Elevations in liver enzymes can occur with ELZONRIS. Grade 3 or higher elevations in liver enzymes occurred in approximately 40% of patients in clinical trials

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

ADVERSE REACTIONS:

The most common adverse reactions in the clinical trials (incidence ≥ 30%) are capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia, and weight increase. The most common laboratory abnormalities (incidence ≥ 50%) are decreases in albumin, platelets, hemoglobin, calcium, 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.
Thank You