BREYANZI® (lisocabtagene maraleucel) Dosing and Administration

INDICATIONS AND USAGE

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

- adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:
    - refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemo-immunotherapy; or
    - refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
    - relapsed or refractory disease after two or more lines of systemic therapy.

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.

- adult patients with relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor. This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

Dose

See the respective Certificate of Release for Infusion (RFI Certificate) for each component, for the actual cell counts and volumes to be infused.

A single dose of BREYANZI contains CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied separately in one to four single-dose vials. See table below for dose range per indication

Indication	BREYANZI Dose Range
LBCL after 2 or more lines of therapy	50 to 110 × 10^6 CAR-positive viable T cells
LBCL after 1 line of therapy	90 to 110 × 10^6 CAR-positive viable T cells
CLL or SLL	

Administration

BREYANZI is for autologous use only. The patient's identity must match the patient identifiers on the BREYANZI cartons, vials and syringe labels. Do not infuse BREYANZI if the information on the patient-specific labels does not match the intended patient.

Preparing the Patient for BREYANZI

Confirm the availability of BREYANZI before starting lymphodepleting chemotherapy.

Pretreatment

Administer the lymphodepleting chemotherapy regimen before infusion of BREYANZI: fludarabine 30 mg/m^2/day intravenously (IV), and cyclophosphamide 300 mg/m^2/day IV for 3 days.

See the prescribing information for fludarabine and cyclophosphamide for information on dose adjustment in renal impairment.

Infuse BREYANZI 2 to 7 days after completion of lymphodepleting chemotherapy.

Delay the infusion of BREYANZI if the patient has unresolved serious adverse events from preceding chemotherapies, active uncontrolled infection, or active graft-versus-host disease (GVHD).

Premedication

To minimize the risk of infusion reactions, premedicate the patient with acetaminophen (650 mg orally) and diphenhydramine (25-50 mg, IV or orally), or another H1-antihistamine, 30 to 60 minutes prior to treatment with BREYANZI.

Avoid prophylactic use of systemic corticosteroids, as they may interfere with the activity of BREYANZI.

Receipt of BREYANZI

- BREYANZI is shipped directly to the cell-associated lab or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper.
- Confirm the patient's identity with the patient identifiers on the shipper.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is qualified for onsite storage, transfer BREYANZI to onsite vapor phase of liquid nitrogen storage prior to preparation.
- If the patient is not expected to be ready for administration before the shipper expires and the infusion site is not qualified for onsite storage, contact Bristol-Myers Squibb at 1-888-805-4555 to arrange for return shipment.

Preparing BREYANZI

***Before** thawing the vials*

- Confirm the patient's identity with the patient identifiers on the RFI Certificate.
- Read the RFI Certificate (affixed inside the shipper) for information on the number of syringes you will need to administer the CD8 and CD4 components (syringe labels are provided with the RFI Certificate). There is a separate RFI Certificate for each cell component.

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Preparing BREYANZI

Before thawing the vials (cont)

- Confirm tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Confirm the infusion time in advance and adjust the start time of BREYANZI thaw such that it will be available for infusion when the patient is ready.

Thawing the vials

1. Confirm the patient's identity with the patient identifiers on the outer carton and on the syringe labels.

   Once the vials of CAR-positive viable T cells (CD8 component and CD4 component) are removed from frozen storage, the thaw must be carried to completion and the cells administered within 2 hours.
2. Remove the CD8 component carton and CD4 component carton from the outer carton.
3. Confirm the patient's identity with the patient identifiers on the inner carton.
4. Open each inner carton and visually inspect the vial(s) for damage. If the vials are damaged, contact Bristol-Myers Squibb at 1-888-805-4555.
5. Confirm the patient's identity with the patient identifiers on the vials.
6. Carefully remove the vials from the cartons, place vials on a protective barrier pad, and thaw at room temperature until there is no visible ice in the vials. Thaw all of the vials at the same time. **Keep the CD8 and CD4 components separate.**

Dose preparation

- Prepare BREYANZI using sterile technique.
- Based on the concentration of CAR-positive viable T cells for each component, more than one vial of each of the CD8 and CD4 components may be required to complete a dose. A separate syringe should be prepared for each CD8 or CD4 component vial received.

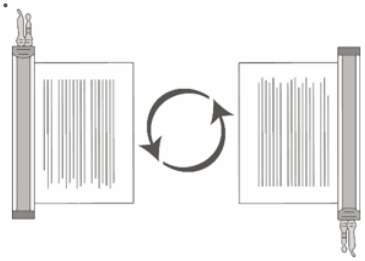
  Note: The volume to be drawn up and infused may differ for each component as indicated on the RFI Certificate. Do NOT draw up excess volume into the syringe.
- Each vial contains 5 mL with a total extractable volume of 4.6 mL of CD8 or CD4 component T cells. The RFI Certificate for each component indicates the volume (mL) of cells to be drawn up into each syringe. Use the smallest Luer-lock tip syringe necessary (1, 3, or 5 mL) to draw up the specified volume from each vial. A 5 mL syringe should not be used for volumes less than 3 mL.

7. **Prepare the syringe(s) of the CD8 component first.** Affix the CD8 syringe labels to the syringe(s) prior to pulling the required volume into the syringe(s).

Note: It is important to confirm that the volume drawn up for each component matches the volume specified in the respective RFI Certificate. Do NOT draw up excess volume into the syringe.

Withdrawal of the required volume of cells from each vial into a separate syringe should be carried out using the following instructions:

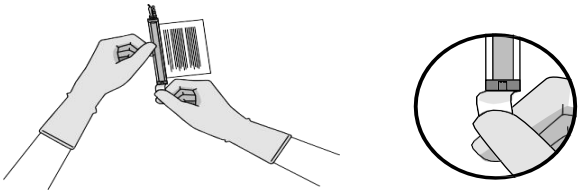
8. Hold the thawed vial(s) upright and gently invert the vial(s) 5 times to mix the cell product. If any clumping is apparent, continue to invert the vial(s) until clumps have dispersed and cells appear to be evenly resuspended.



Vial upright → Vial inverted

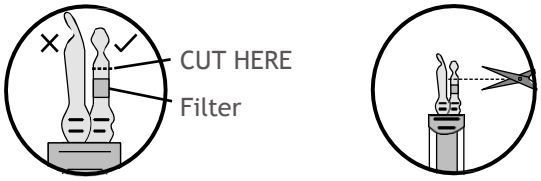
9. Visually inspect the thawed vial(s) for damage or leaks. Do not use if the vial is damaged or if the clumps do not disperse; contact Bristol-Myers Squibb at 1-888-805-4555. The liquid in the vials should be slightly opaque to opaque, colorless to yellow or brownish-yellow.
10. Remove the polyaluminum cover (if present) from the bottom of the vial and swab the septum with an alcohol wipe. Allow to air dry before proceeding.

    NOTE: The absence of the polyaluminum cover does not impact the sterility of the vial.



11. Keeping the vial(s) upright, cut the seal on the tubing line on the top of the vial immediately above the filter to open the air vent on the vial.

    NOTE: Be careful to select the correct tubing line with the filter. Cut ONLY the tubing with a filter.



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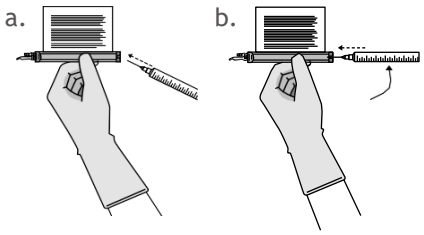
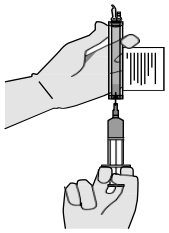
12. Hold a 20-gauge, 1-1 ½ inch needle, with the opening of the needle tip away from the retrieval port septum.
    a. Insert the needle into the septum at a 45°- 60° angle to puncture the retrieval port septum.
    b. Increase the angle of the needle gradually as the needle enters the vial.



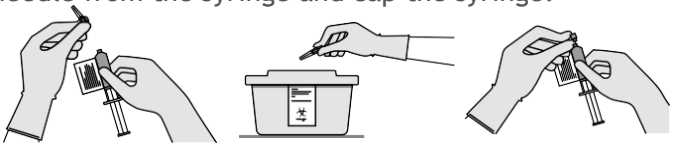
13. WITHOUT drawing air into the syringe, slowly withdraw the target volume (as specified in the RFI Certificate).

    Carefully inspect the syringe for signs of debris prior to proceeding. If there is debris, contact Bristol-Myers Squibb at 1-888-805-4555.



14. Verify that the volume of CD8/CD4 component matches the volume specified for the relevant component in the RFI Certificate.

    Once the volume is verified, remove the syringe/needle from the vial, carefully detach the needle from the syringe and cap the syringe.



15. Continue to keep the vial horizontal and return it to the carton to avoid leaking from the vial.
16. Dispose of any unused portion of BREYANZI (according to local biosafety guidelines).
17. Repeat the process steps 7-16 for the CD4 Component.
18. Transport the labeled CD8 and CD4 syringes to the bedside by placing with protective barrier pad inside an insulated room temperature container.

<u>BREYANZI Administration</u>

- **Do NOT** use a leukodepleting filter.
- Ensure tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Confirm the patient's identity matches the patient identifiers on the syringe label.
- Once BREYANZI has been drawn into syringes, proceed with administration as soon as possible. The total time from removal from frozen storage to patient administration should not exceed 2 hours as indicated by the time entered on the syringe label.

1. Use intravenous normal saline to flush all the infusion tubing prior to and after each CD8 or CD4 component administration.
2. Administer the entire volume of the CD8 component intravenously at an infusion rate of approximately 0.5 mL/minute, using the closest port or Y-arm.

   NOTE: The time for infusion will vary but will usually be less than 15 minutes for each component.
3. If more than one syringe is required for a full cell dose of the CD8 component, administer the volume in each syringe consecutively without any time between administering the contents of the syringes (unless there is a clinical reason (e.g., infusion reaction) to hold the dose).
4. After the CD8 component has been administered, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.
5. Administer the CD4 component second, immediately after administration of the CD8 component is complete, using steps 1-4, as described for the CD8 component. Following administration of the CD4 component, flush the tubing with normal saline, using enough volume to clear the tubing and the length of the IV catheter.

BREYANZI contains human blood cells that are genetically modified with replication-incompetent, self-inactivating lentiviral vector. Follow universal precautions and local biosafety guidelines applicable for the handling and disposal, to avoid potential transmission of infectious diseases.

IMPORTANT SAFETY INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, AND SECONDARY HEMATOLOGICAL MALIGNANCIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving BREYANZI. Do not administer BREYANZI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving BREYANZI, including concurrently with CRS, after CRS resolution or in the absence of CRS. Monitor for neurologic events after treatment with BREYANZI. Provide supportive care and/or corticosteroids as needed.
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including BREYANZI.
- BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS.

BREYANZI® (lisocabtagene maraleucel) Dosing and Administration (*continued*)

CYTOKINE RELEASE SYNDROME

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with BREYANZI.

Among patients receiving BREYANZI for LBCL (N=418), CRS occurred in 46% (190/418), including ≥Grade 3 CRS (Lee grading system) in 3.1% of patients.

In patients receiving BREYANZI after two or more lines of therapy for LBCL, CRS occurred in 46% (122/268), including ≥ Grade 3 CRS in 4.1% of patients. One patient had fatal CRS and 2 had ongoing CRS at time of death. The median time to onset was 5 days (range: 1 to 15 days). CRS resolved in 98% with a median duration of 5 days (range: 1 to 17 days).

In patients receiving BREYANZI after one line of therapy for LBCL, CRS occurred in 45% (68/150), including Grade 3 CRS in 1.3% of patients. The median time to onset was 4 days (range: 1 to 63 days). CRS resolved in all patients with a median duration of 4 days (range: 1 to 16 days).

Among patients receiving BREYANZI for CLL/SLL, CRS occurred in 83% (74/89), including Grade 3 CRS in 9% of patients. The median time to onset was 4 days (range: 1 to 18 days). CRS resolved in 97% with a median duration of 6 days (range: 2 to 37 days).

The most common manifestations of CRS (≥10% in LBCL or CLL/SLL) included fever (94% LBCL; 97% CLL/SLL), hypotension (42% LBCL; 46% CLL/SLL), tachycardia (28% LBCL; 8% CLL/SLL), chills (23% LBCL; 43% CLL/SLL), hypoxia (16% LBCL; 35% CLL/SLL), sinus tachycardia (22% CLL/SLL), and headache (12% LBCL; 18% CLL/SLL).

Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, diffuse alveolar damage, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome(HLH/MAS).

Ensure that 2 doses of tocilizumab are available prior to infusion of BREYANZI.

Of the patients who received BREYANZI for LBCL (n=418) and CLL/SLL (n=89), 23% (LBCL) and 64% (CLL/SLL) received tocilizumab and/or a corticosteroid for CRS, including 10% (LBCL) and 33% (CLL/SLL) who received tocilizumab only and 2.2% (LBCL) and 2.2% (CLL/SLL) who received corticosteroids only.

NEUROLOGIC TOXICITIES

Neurologic toxicities that were fatal or life-threatening, including immune effector cell-associated neurotoxicity syndrome (ICANS), occurred following treatment with BREYANZI. Serious events including cerebral edema and seizures occurred with BREYANZI. Fatal and serious cases of leukoencephalopathy, some attributable to fludarabine, also occurred.

In patients receiving BREYANZI after two or more lines of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred in 35% (95/268), including ≥ Grade 3 in 12% of patients. Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death.

The median time to onset of neurotoxicity was 8 days (range: 1 to 46 days). Neurologic toxicities resolved in 85% with a median duration of 12 days (range: 1 to 87 days).

In patients receiving BREYANZI after one line of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred in 27% (41/150) of patients, including Grade 3 cases in 7% of patients. The median time to onset of neurologic toxicities was 8 days (range: 1 to 63 days). The median duration of neurologic toxicity was 6 days (range: 1 to 119 days).

In all patients combined receiving BREYANZI for LBCL, CAR T cell-associated neurologic toxicities occurred in 33% (136/418), including ≥ Grade 3 cases in 10% of patients. The median time to onset was 8 days (range: 1 to 63), with 87% of cases developing by 16 days. Neurologic toxicities resolved in 85% of patients with a median duration of 11 days (range: 1 to 119 days). Of patients developing neurotoxicity, 77% (105/136) also developed CRS.

In patients receiving BREYANZI for CLL/SLL, CAR T cell-associated neurologic toxicities occurred in 46% (41/89), including Grade 3 cases in 20% of patients and a single Grade 4 case. The median time to onset of neurotoxicity was 7 days (range: 1 to 21 days), with 95% of cases developing by 16 days. Neurologic toxicities resolved in 85% with a median duration of 7 days (range: 1 to 83 days). Of patients developing neurotoxicity, 95% (39/41) also developed CRS.

The most common neurologic toxicities (≥5% in LBCL or CLL) included encephalopathy (20% LBCL; 36% CLL/SLL), tremor (13% LBCL; 14% CLL/SLL), aphasia (8% LBCL; 8% CLL/SLL), headache (6% LBCL; 9% CLL/SLL), dizziness (6% LBCL), and delirium (5% LBCL; 12% CLL/SLL).

CRS AND NEUROLOGIC TOXICITIES MONITORING

Monitor patients daily for at least 7 days following BREYANZI infusion at a REMS-certified healthcare facility for signs and symptoms of CRS and neurologic toxicities and assess for other causes of neurological symptoms. Monitor patients for signs and symptoms of CRS and neurologic toxicities for at least 4 weeks after infusion and treat promptly. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated. Manage neurologic toxicity with supportive care and/or corticosteroid as needed. Counsel patients to seek immediate medical attention should signs or symptoms of CRS or neurologic toxicity occur at any time.

BREYANZI REMS

Because of the risk of CRS and neurologic toxicities, BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS. The required components of the BREYANZI REMS are:

- Healthcare facilities that dispense and administer BREYANZI must be enrolled and comply with the REMS requirements
- Certified healthcare facilities must have on-site, immediate access to tocilizumab
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after BREYANZI infusion, if needed for treatment of CRS

Further information is available at www.BreyanziREMS.com, or contact Bristol-Myers Squibb at 1-888-423-5436.

HYPERSENSITIVITY REACTIONS

Allergic reactions may occur with the infusion of BREYANZI. Serious hypersensitivity reactions, including anaphylaxis, may be due to dimethyl sulfoxide (DMSO).

SERIOUS INFECTIONS

Severe infections, including life-threatening or fatal infections, have occurred in patients after BREYANZI infusion.

In patients receiving BREYANZI, infections of any grade occurred in 36% (LBCL) and 35% (CLL/SLL), with Grade 3 or higher infections occurred in 12% (LBCL) and 16% (CLL/SLL) of all patients. Grade 3 or higher infections with an unspecified pathogen occurred in 7% (LBCL) and 10% (CLL/SLL), bacterial infections in 4.3% (LBCL) and 2.2% (CLL/SLL), viral infections in 1.9% (LBCL) and 1.1% (CLL/SLL), and fungal infections in 0.5% (LBCL) and 2.2% (CLL/SLL).

Febrile neutropenia developed after BREYANZI infusion in 8% (LBCL) and 12% (CLL/SLL) of patients. Febrile neutropenia may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids, and other supportive care as medically indicated.

Monitor patients for signs and symptoms of infection before and after BREYANZI administration and treat appropriately. Administer prophylactic antimicrobials according to standard institutional guidelines.

BREYANZI® (lisocabtagene maraleucel) Dosing and Administration (*continued*)

Avoid administration of BREYANZI in patients with clinically significant, active systemic infections.

Viral Reactivation: Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells.

In patients who received BREYANZI, 15 of 16 LBCL patients, and all 9 CLL/SLL patients with a prior history of HBV were treated with concurrent antiviral suppressive therapy. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing. In patients with prior history of HBV, consider concurrent antiviral suppressive therapy to prevent HBV reactivation per standard guidelines.

PROLONGED CYTOPENIAS

Patients may exhibit cytopenias not resolved for several weeks following lymphodepleting chemotherapy and BREYANZI infusion.

Grade 3 or higher cytopenias persisted at Day 29 following BREYANZI infusion in 36% (LBCL) and 45% (CLL/SLL) of patients, and included thrombocytopenia in 28% (LBCL) and 23% (CLL/SLL), neutropenia in 21% (LBCL) and 35% (CLL/SLL), and anemia in 6% (LBCL) and 12% (CLL/SLL).

Monitor complete blood counts prior to and after BREYANZI administration.

HYPOGAMMAGLOBULINEMIA

B-cell aplasia and hypogammaglobulinemia can occur in patients receiving treatment with BREYANZI.

In patients receiving BREYANZI, hypogammaglobulinemia was reported as an adverse reaction in 11% (LBCL) and 14% (CLL/SLL) of patients. Hypogammaglobulinemia, either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion, was reported in 28% (LBCL) and 37% (CLL/SLL) of patients.

Monitor immunoglobulin levels after treatment with BREYANZI and manage using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement as clinically indicated.

Live vaccines: The safety of immunization with live viral vaccines during or following BREYANZI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during BREYANZI treatment, and until immune recovery following treatment with BREYANZI.

SECONDARY MALIGNANCIES

Patients treated with BREYANZI may develop secondary malignancies. T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including BREYANZI. Mature T cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusion, and may include fatal outcomes. Monitor lifelong for secondary malignancies. In the event that a secondary malignancy occurs, contact Bristol-Myers Squibb at 1-888-805-4555 for reporting and to obtain instructions on collection of patient samples for testing.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to the potential for neurologic events, including altered mental status or seizures, patients receiving BREYANZI are at risk for developing altered or decreased consciousness or impaired coordination in the 8 weeks following BREYANZI administration. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks.

IMMUNE EFFECTOR CELL-ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS-LIKE SYNDROME (IEC-HS)

Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome (IECHS), including fatal or life-threatening reactions, occurred following treatment with BREYANZI. Three of 89 (3%) safety evaluable patients with R/R CLL/SLL developed IEC-HS. Time to onset of IEC-HS ranged from 7 to 18 days. Two of the 3 patients developed IEC-HS in the setting of ongoing CRS and 1 in the setting of ongoing neurotoxicity. IEC-HS was fatal in 2 of 3 patients. One patient had fatal IEC-HS and one had ongoing IEC-HS at time of death. IEC-HS is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of IEC-HS should be administered per current practice guidelines.

ADVERSE REACTIONS

The most common nonlaboratory adverse reactions (incidence ≥ 30%) in:

- LBCL are fever, cytokine release syndrome, fatigue, musculoskeletal pain, and nausea. The most common Grade 3-4 laboratory abnormalities (≥ 30%) include lymphocyte count decrease, neutrophil count decrease, platelet count decrease, and hemoglobin decrease.
- CLL/SLL are cytokine release syndrome, encephalopathy, fatigue, musculoskeletal pain, nausea, and diarrhea. The most common Grade 3-4 laboratory abnormalities (≥ 30%) in CLL/SLL include neutrophil count decrease, white blood cell decrease, hemoglobin decrease, platelet count decrease, and lymphocyte count decrease.

Please see full Prescribing Information**, including Boxed WARNINGS and** Medication Guide**.**

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