

Breyanzi® (lisocabtagene maraleucel) Suspension for IV Infusion Coverage Policy Considerations*

***This content is intended for decision-makers associated with payers, formulary committees, or similar entities. It is intended to provide relevant background (pages 1-5) and example coverage policy language for Breyanzi (page 6) based on the FDA-approved Prescribing Information. This document is not meant to provide clinical advice or clinical direction concerning Breyanzi or any pharmaceutical product or medical procedure.**

Breyanzi is a CAR T cell therapy indicated for 4 distinct adult populations across R/R NHL subtypes¹:

R/R CLL or SLL	<ul style="list-style-type: none"> • After ≥2 prior lines of therapy, including a BTKi and BCL2i (based on the TRANSCEND CLL 004 trial)
R/R LBCL	<ul style="list-style-type: none"> • ≤12 months after first-line chemoimmunotherapy (based on the TRANSFORM and PILOT trials) • After first-line chemoimmunotherapy and ineligible for transplant (based on the PILOT trial) • After ≥2 lines of systemic therapy (based on the TRANSCEND trial)

BCL2i=B-cell lymphoma 2 inhibitor; BTKi=Bruton tyrosine kinase inhibitor; CAR=chimeric antigen receptor; FDA=US Food and Drug Administration; IV=intravenous; R/R CLL or SLL=relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma; R/R LBCL=relapsed or refractory large B-cell lymphoma; R/R NHL=relapsed or refractory non-Hodgkin lymphoma.

INDICATION

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 chemoimmunotherapy; 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).

SELECT 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.**

Please see additional Important Safety Information on pages 7-11 and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

Breyanzi® (lisocabtagene maraleucel) Coverage Policy Considerations*

*This content is intended for decision-makers associated with payers, formulary committees, or similar entities. It is intended to provide relevant background (pages 1-5) and example coverage policy language for Breyanzi (page 6) based on the FDA-approved Prescribing Information. This document is not meant to provide clinical advice or clinical direction concerning Breyanzi or any pharmaceutical product or medical procedure.

Breyanzi is administered as a one-time infusion[†] in an inpatient or outpatient setting¹

- Breyanzi treatment is part of a larger CAR T process that includes leukapheresis, manufacturing, administration, and monitoring¹
- Breyanzi must be administered at a REMS-certified healthcare facility¹
- BMS and the FDA do not require FACT accreditation¹
- Non-hospital, independent community clinic sites are activated to deliver Breyanzi in partnership with a designated AE hospital

CMS has issued a national coverage determination (NCD) for CAR T cell therapies for cancer²

- CMS covers autologous CAR T cell therapy when^{2,3}:
 - Administered at a healthcare facility certified by the respective manufacturer under the applicable REMS program (not limited to hospital sites; FACT accreditation not required)
 - Used for a medically accepted indication (ie, FDA-approved indication or use supported in CMS-approved compendia)

R/R CLL or SLL: TRANSCEND CLL 004 evaluated Breyanzi in a single-arm trial with a broad range of patients who received ≥2 prior lines of therapy, including a BTKi and BCL2i (N=89)¹

- Patient eligibility was based on^{1,4†}:

SELECT INCLUSION CRITERIA	SELECT EXCLUSION CRITERIA
<ul style="list-style-type: none">• ECOG performance status ≤1• Prior autologous or allogeneic HSCT was allowed[§]	<ul style="list-style-type: none">• Creatinine clearance <30 mL/min• ALT >5 times the upper limit of normal[¶]• Left ventricular ejection fraction <40%

- There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy¹

[†]A single dose of Breyanzi contains CAR-positive viable T cells that consist of CD8 and CD4 components, with each component supplied separately in 1 to 4 single-dose vials. For R/R CLL or SLL or R/R LBCL after 1 line of therapy, a single dose contains 90 to 110 x 10⁶ CAR-positive viable T cells. For R/R LBCL after ≥2 lines of therapy, a single dose contains 50 to 110 x 10⁶ CAR-positive viable T cells.¹

[‡]Additional eligibility criteria applied.

[§]Patients were excluded if they had prior allogeneic HSCT within 100 days before leukapheresis.⁴

[¶]Patients with leukemic infiltration of the liver were not excluded.¹

AE=adverse event; ALT=alanine aminotransferase; BCL2i=B-cell lymphoma 2 inhibitor; BTKi=Bruton tyrosine kinase inhibitor; CAR=chimeric antigen receptor; CMS=Centers for Medicare & Medicaid Services; ECOG=Eastern Cooperative Oncology Group; FACT=Foundation for the Accreditation of Cellular Therapy; FDA=US Food and Drug Administration; HSCT=hematopoietic stem cell transplant; REMS=Risk Evaluation and Mitigation Strategy; R/R CLL or SLL=relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma; R/R LBCL=relapsed or refractory large B-cell lymphoma.

SELECT IMPORTANT SAFETY INFORMATION

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 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).

Please see additional Important Safety Information on pages 7-11 and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

Breyanzi® (lisocabtagene maraleucel) Coverage Policy Considerations*

*This content is intended for decision-makers associated with payers, formulary committees, or similar entities. It is intended to provide relevant background (pages 1-5) and example coverage policy language for Breyanzi (page 6) based on the FDA-approved Prescribing Information. This document is not meant to provide clinical advice or clinical direction concerning Breyanzi or any pharmaceutical product or medical procedure.

2L LBCL transplant-eligible: TRANSFORM evaluated Breyanzi head-to-head versus standard therapy consisting of 3 cycles of chemoimmunotherapy followed by high-dose therapy and autologous HSCT in patients with LBCL who were R/R ≤12 months after first-line therapy (N=184)¹

- Patient eligibility was based on^{1,5†}:

SELECT INCLUSION CRITERIA	SELECT EXCLUSION CRITERIA
<ul style="list-style-type: none"> • Potential candidate for HSCT • ECOG performance status ≤1[‡] • Secondary CNS lymphoma involvement 	<ul style="list-style-type: none"> • Creatinine clearance <45 mL/min • ALT >5 times the upper limit of normal • Left ventricular ejection fraction <40% • Absolute neutrophil count <1.0 x 10⁹ cells/L or platelets <50 x 10⁹ cells/L in the absence of bone marrow involvement

- In TRANSFORM, eligibility criteria required adequate organ function and blood counts for HSCT¹

2L LBCL transplant-ineligible: PILOT evaluated Breyanzi in a single-arm trial after failure of frontline chemoimmunotherapy, regardless of time to relapse (N=61)¹

- Patient eligibility was based on^{1,6†}:

SELECT INCLUSION CRITERIA	SELECT EXCLUSION CRITERIA
<ul style="list-style-type: none"> • Not eligible for HSCT per trial criteria[§] • ECOG performance status ≤2 • Secondary CNS lymphoma involvement 	<ul style="list-style-type: none"> • ECOG performance status >2 • Creatinine clearance ≤30 mL/min • ALT/AST >5 times the upper limit of normal • Left ventricular ejection fraction <40%

- There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy¹

[†]Additional eligibility criteria applied.

[‡]After screening in the TRANSFORM trial, 3 patients deteriorated and had ECOG performance status of 2 at baseline.⁷

[§]In PILOT, patients were considered transplant ineligible if they met ≥1 of the following criteria: age ≥70 years, adjusted diffusing capacity of the lung for carbon monoxide ≤60%, left ventricular ejection fraction <50%, creatinine clearance <60 mL/min, ALT/AST >2 times the upper limit of normal, ECOG performance status=2.¹

2L=second line; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; FDA=US Food and Drug Administration; HSCT=hematopoietic stem cell transplant; LBCL=large B-cell lymphoma; R/R=relapsed or refractory.

SELECT IMPORTANT SAFETY INFORMATION

Cytokine Release Syndrome (cont'd)

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), chills (23% LBCL; 43% CLL/SLL), hypoxia (16% LBCL; 35% CLL/SLL), sinus tachycardia (22% CLL/SLL), and headache (12% LBCL; 18% CLL/SLL).

Please see additional Important Safety Information on pages 7-11 and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

Breyanzi® (lisocabtagene maraleucel) Coverage Policy Considerations*

***This content is intended for decision-makers associated with payers, formulary committees, or similar entities. It is intended to provide relevant background (pages 1-5) and example coverage policy language for Breyanzi (page 6) based on the FDA-approved Prescribing Information. This document is not meant to provide clinical advice or clinical direction concerning Breyanzi or any pharmaceutical product or medical procedure.**

3L+ LBCL: TRANSCEND was the largest pivotal trial with a broad range of patients (N=269)⁸

- Patient eligibility was based on^{1†}:

SELECT INCLUSION CRITERIA	SELECT EXCLUSION CRITERIA
ECOG performance status ≤ 2 [‡]	Creatinine clearance < 30 mL/min
Prior autologous or allogeneic HSCT [§]	ALT > 5 times the upper limit of normal
Secondary CNS lymphoma involvement [¶]	Left ventricular ejection fraction $< 40\%$

- There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy¹

[†]Additional eligibility criteria applied.

[‡]Among enrolled patients, 98.5% had an ECOG score of 0-1 and 1.5% had an ECOG score of 2.¹

[§]Among enrolled patients, 37% had prior HSCT.¹

[¶]Among enrolled patients, 3% had secondary CNS lymphoma involvement.¹

3L+=third or subsequent line; ALT=alanine aminotransferase; CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; FDA=US Food and Drug Administration; HSCT=hematopoietic stem cell transplant; LBCL=large B-cell lymphoma.

SELECT IMPORTANT SAFETY INFORMATION

Cytokine Release Syndrome (cont'd)

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 \geq Grade 3 cases 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% of patients 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 toxicity 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 \geq 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.

Please see additional Important Safety Information on pages 7-11 and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

References: 1. Breyanzi [package insert]. Summit, NJ: Bristol-Myers Squibb Company; 2024. 2. CMS. NCD - chimeric antigen receptor (CAR) T-cell therapy (110.24). Accessed December 1, 2023. <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=374&ncdver=1> 3. CMS. Chimeric antigen receptor (CAR) T-cell therapy for cancers CAG-00451N. Accessed December 1, 2023. <https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=291> 4. Siddiqi T, Maloney DG, Kenderian SS, et al. Lisocabtagene maraleucel in chronic lymphocytic leukaemia and small lymphocytic lymphoma (TRANSCEND CLL 004): a multicentre, open-label, single-arm, phase 1-2 study. *Lancet*. 2023;402(10402):641-654. 5. Kamdar M, Solomon SR, Armason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. *Lancet*. 2022;399:2294-2308. 6. Sehgal A, Hoda D, Riedell P, et al. Lisocabtagene maraleucel as second-line therapy for relapsed or refractory large B-cell lymphoma in patients not intended for hematopoietic stem cell transplantation: primary analysis from the phase 2 PILOT study. Presented at: American Society of Clinical Oncology (ASCO); June 3-7, 2022. 7. Data on file. BMS-REF-LIS-0021. Princeton, NJ: Bristol-Myers Squibb Company; 2022. 8. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicenter seamless design study. *Lancet*. 2020;396(10254):839-852.

Please see Important Safety Information on pages 7-11 and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

Example Coverage Policy for Breyanzi® (lisocabtagene maraleucel)*

*This content is intended for decision-makers associated with payers, formulary committees, or similar entities. It is intended to provide relevant background (pages 1-5) and example coverage policy language for Breyanzi (page 6) based on the FDA-approved Prescribing Information. This document is not meant to provide clinical advice or clinical direction concerning Breyanzi or any pharmaceutical product or medical procedure.

POLICY

This policy is designed to address the appropriate use of Breyanzi according to FDA-approved product labeling. Each member's unique clinical characteristics may warrant individual consideration, based on review of applicable medical records. Policy coverage is subject to the specific terms of the member's benefit plan.

CRITERIA FOR AUTHORIZATION

Authorization may be granted for a one-time treatment of members when the following criteria are met:

- Age ≥18 years old
- Diagnosed with one of the following:
 - R/R CLL or SLL
 - After ≥2 prior lines of therapy, including a BTKi and BCL2i (patients may have received prior autologous or allogeneic HSCT)
 - R/R LBCL, including subtypes listed below[†]:
 - Within 12 months of first-line chemoimmunotherapy
 - After first-line chemoimmunotherapy and are not eligible for transplant
 - After ≥2 lines of systemic therapy (patients may have received prior autologous or allogeneic HSCT)
- ECOG performance status ≤2
- Creatinine clearance ≥30 mL/min
- Adequate bone marrow function, as determined by the treating physician
- Left ventricular ejection fraction ≥40%
- Aminotransferase enzyme(s) ≤5 times the upper limit of normal
- No primary CNS lymphoma (authorized patients may have secondary CNS lymphoma involvement)
- No active infection or inflammatory disorders
- Treatment at a healthcare facility certified by the manufacturer based on the REMS requirements defined by the FDA

POLICY NOTES:

For Medicare beneficiaries, covered use is consistent with the applicable national coverage determination (NCD) issued by the Centers for Medicare & Medicaid Services (CMS). For details on the final NCD decision, please visit: <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=374&ncdver=1>.

[†]LBCL subtypes include DLBCL not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal LBCL, and follicular lymphoma grade 3B.

BCL2i=B-cell lymphoma 2 inhibitor; BTKi=Bruton tyrosine kinase inhibitor; CNS=central nervous system; DLBCL=diffuse large B-cell lymphoma; ECOG=Eastern Cooperative Oncology Group; FDA=US Food and Drug Administration; HSCT=hematopoietic stem cell transplant; REMS=Risk Evaluation and Mitigation Strategy; R/R CLL or SLL=relapsed or refractory chronic lymphocytic leukemia or small lymphocytic lymphoma; R/R LBCL=relapsed or refractory large B-cell lymphoma.

SELECT IMPORTANT SAFETY INFORMATION

Neurologic Toxicities (cont'd)

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).

Please see additional Important Safety Information on pages 7-11 and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

INDICATION

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 chemoimmunotherapy; 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).

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.**

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 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).

Please see additional Important Safety Information on next page and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

IMPORTANT SAFETY INFORMATION (cont'd)

Cytokine Release Syndrome (cont'd)

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 ($\geq 10\%$ in LBCL or CLL/SLL) included fever (94% LBCL; 97% CLL/SLL), hypotension (42% LBCL; 46% CLL/SLL), tachycardia (28% LBCL), 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 \geq Grade 3 cases 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% of patients 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 toxicity 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 \geq 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 ($\geq 5\%$ 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).

Please see additional Important Safety Information on next page and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

IMPORTANT SAFETY INFORMATION (cont'd)

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 1-866-340-7332.

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 occurring 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. 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.

Please see additional Important Safety Information on next page and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

IMPORTANT SAFETY INFORMATION (cont'd)

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 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 (IEC-HS), 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.

Please see additional Important Safety Information on next page and full [Prescribing Information](#), including **Boxed WARNINGS** and Medication Guide.

IMPORTANT SAFETY INFORMATION (cont'd)

Adverse Reactions

The most common nonlaboratory adverse reactions (incidence $\geq 30\%$) in:

- LBCL are fever, cytokine release syndrome, fatigue, musculoskeletal pain, and nausea. The most common Grade 3-4 laboratory abnormalities ($\geq 30\%$) 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 ($\geq 30\%$) 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.