



Breyanzi® Product Information

**NEW INDICATION
IN R/R CLL OR SLL**

Indication¹	<p>BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:</p> <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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. <p><u>Limitations of Use:</u> BREYANZI is not indicated for the treatment of patients with primary central nervous system lymphoma.</p> <ul style="list-style-type: none"> 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. <p>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).</p>
Dose¹	<p>A single dose of Breyanzi contains CAR-positive viable T cells that consist of CD8 and CD4 components, with each component supplied separately in one to four single-dose vials:</p> <p>For R/R CLL or SLL, or R/R LBCL after 1 line of therapy: 90 to 110 x 10⁶ CAR-positive viable T cells</p> <p>For R/R LBCL after ≥2 lines of therapy: 50 to 110 x 10⁶ CAR-positive viable T cells</p>
Dosage Form¹	<p>Outer carton containing:</p> <ul style="list-style-type: none"> Carton for CD8 component, with up to 4 single-dose vials Carton for CD4 component, with up to 4 single-dose vials
NDC¹	<p>10-digit format: 73153-900-01 11-digit format: 73153-0900-01</p>
WAC²	\$487,477.43*

*Effective as of 1/1/2024. WAC price does not include confidential discounts, which may exist in the marketplace.

CAR=chimeric antigen receptor; NDC=National Drug Code; 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; WAC=wholesale acquisition cost.

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.**

HCPCS Level II Product Code³

HCPCS Code	Description	Effective Date
Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-CD19 CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per therapeutic dose	October 1, 2021

ICD-10-CM Diagnosis Codes⁴

Adult Patients With R/R LBCL After First-Line Chemoimmunotherapy or ≥2 Lines of Systemic Therapy

ICD-10-CM Code Range	Description
C82.4_	Follicular lymphoma grade IIIb
C83.3_	Diffuse large B-cell lymphoma
C83.9_	Non-follicular (diffuse) lymphoma, unspecified
C85.1_	Unspecified B-cell lymphoma
C85.2_	Mediastinal (thymic) large B-cell lymphoma
C85.8_	Other specified types of non-Hodgkin lymphoma
Z51.12	Encounter for antineoplastic immunotherapy

Adult Patients With R/R CLL or SLL After ≥ 2 Prior Lines of Therapy, Including a BTKi and BCL2i

ICD-10-CM Code Range	Description
C83.0_ CODES	Small cell B-cell lymphoma
C91.10 FOR NEW	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12 INDICATION	Chronic lymphocytic leukemia of B-cell type in relapse
Z51.12 IN R/R CLL OR SLL	Encounter for antineoplastic immunotherapy

BCL2i=B-cell lymphoma 2 inhibitor; BTKi=Bruton tyrosine kinase inhibitor; CAR=chimeric antigen receptor; HCPCS=Healthcare Common Procedure Coding System; ICD-10-CM=International Classification of Diseases, Tenth Revision, Clinical Modification; 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.

Relevant Codes for Breyanzi® (cont'd)

ICD-10-PCS Inpatient Procedure Codes⁵

ICD-10-PCS Code	Description	Effective Date
XW033N7	Introduction of lisocabtagene maraleucel immunotherapy into peripheral vein, percutaneous approach, new technology group 7	October 1, 2021
XW043N7	Introduction of lisocabtagene maraleucel immunotherapy into central vein, percutaneous approach, new technology group 7	

For FY 2024, the ICD-10-PCS codes XW033N7 and XW043N7 are assigned to MS-DRG 018 (Chimeric Antigen Receptor [CAR] T-cell and Other Immunotherapies).⁶

FY=fiscal year; ICD-10-PCS=International Classification of Diseases, Tenth Revision, Procedure Coding System; MS-DRG=Medicare Severity-Diagnosis Related Group.

References:

1. Breyanzi [package insert]. Summit, NJ: Bristol-Myers Squibb Company; 2024.
2. Merative Micromedex RED BOOK. Accessed January 4, 2024. <https://www.micromedexsolutions.com/home/dispatch>
3. CMS. HCPCS quarterly update. Updated October 2023. Accessed October 11, 2023. <https://www.cms.gov/medicare/coding/hcpcsreleasecodesets/hcpcs-quarterly-update>
4. CMS. 2023 ICD-10-CM tabular list of diseases and injuries. Updated January 11, 2023. Accessed September 27, 2023. <https://www.cms.gov/medicare/coding-billing/icd-10-codes/2023-icd-10-cm>
5. CMS. *Fed Regist*. August 13, 2021. IPPS FY 2022 Final Rules. 2021;86(154):44774-45615.
6. CMS. *Fed Regist*. August 28, 2023. IPPS FY 2024 Final Rule. 2023;88(165):58640-59438.

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 \geq 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 \geq 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 (\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).

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.

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).

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.

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.

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.