Medical Drug Clinical Criteria

Subject:	Breyanzi (lisocabtagene maraleucel)		
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Overview

This document addresses the use of Breyanzi (lisocabtagene maraleucel), a CD19-directed immunotherapy, for treatment of relapsed or refractory large B-cell lymphomas.

The FDA approved indications 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

Breyanzi is the third CAR-T therapy indicated for large B-cell lymphoma, following Yescarta (axicabtagene ciloleucel) and Kymriah (tisagenlecleucel).

Breyanzi is also FDA indicated for the treatment of 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.

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy. FDA approval stems from a global Phase 2, open-label, single-arm, multicohort, multicenter study with relapsed/refractory Follicular lymphoma or Marginal zone lymphoma individuals.

Of note, both TRANSCEND trials included follicular lymphoma individuals. TRANSCEND-NHL-001 included follicular lymphoma Grade 3B and TRANSCEND-FL included those with follicular lymphoma Grade 1, 2 or 3a.

In addition, Breyanzi is FDA indicated in adult patients with relapsed or refractory mantle cell lymphoma (MCL). The efficacy of Breyanzi was evaluated in an open-label, multicenter, single-arm trial (TRANSCEND-MCL Cohort; NCT02631044) in adult patients with relapsed or refractory MCL who had received at least two prior lines of therapy including a BTK inhibitor, an alkylating agent, and an anti-CD20 agent.

Breyanzi (lisocabtagene maraleucel, also called liso-cel) is a CD19-directed, genetically-modified autologous T-cell immunotherapy, also known as chimeric antigen receptor (CAR) T-cell therapy. CAR T-cells are made by first collecting T-cells from the patient. The cells are then sent to a laboratory where they are genetically engineered to produce chimeric antigen receptors. The modified T-cells, now known as CAR T-cells, have the ability to better recognize an antigen (the CD19 protein) on targeted tumor cells. After the CAR T-cells have multiplied in the laboratory, they are then infused back into the patient. The modified CAR T-cells help the body's immune system better target and treat the tumor cells.

Breyanzi has a black box warning for cytokine release syndrome (CRS) and should not be administered in patients with active infection or inflammatory disorders due to risk of life-threatening reactions and death. Severe or life-

threatening CRS should be treated with tocilizumab with or without corticosteroids. Breyanzi also has black box warning for causing neurological toxicities, which could also be severe and life-threatening. Monitoring for neurological events after administration is recommended. Breyanzi also has a black box warning for secondary hematological malignancies. T-cell malignancies have occurred following treatment. Due to these black box warnings, Breyanzi is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.

The National Comprehensive Cancer Network® (NCCN) provides additional recommendations with a category 2A level of evidence for the following uses:

- Primary Mediastinal Large B-Cell Lymphoma
- Diffuse Large B-Cell Lymphoma
- Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma
- High-Grade B-Cell Lymphomas
- HIV-Related B-Cell Lymphomas
- Post-Transplant Lymphoproliferative Disorders

Definitions and Measures

Allogeneic cells: Harvested from a histocompatible donor.

Autologous cells: Harvested from the individual's own cells.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemotherapy: The medical treatment of a disease, particularly cancer, with drugs or other chemicals.

Chimerism: Cell populations derived from different individuals; may be mixed or complete.

Complete Response (CR): The disappearance of all signs of cancer as a result of treatment; also called complete remission; does not indicate the cancer has been cured.

Cytotoxic: Treatment that is destructive to cells, preventing their reproduction or growth.

ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.

Line of Therapy:

- First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
- Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
- Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.

Refractory Disease: Illness or disease that does not respond to treatment.

Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Breyanzi (lisocabtagene maraleucel)
Requests for Breyanzi (lisocabtagene maraleucel) for **large B-cell lymphoma** may be approved if the following criteria are met:

I. Individual is 18 years of age or older; **AND**
II. Individual has a histologically confirmed diagnosis of one of the following:
  A. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NCCN 1A, 2A); **OR**
  B. Transformed DLBCL from indolent histology; **OR**
  C. High-grade B-cell lymphoma; **OR**
  D. Primary mediastinal large B-cell lymphoma; **OR**
  E. Follicular lymphoma; **OR**
  F. Mantle cell lymphoma; **OR**
  G. HIV Related B-Cell Lymphomas (NCCN 2A); **OR**
  H. Monomorphic Post-Transplant Lymphoproliferative (B-cell type) Disorders (PTLD) (NCCN 2A); **AND**
III. Is using in one of the following ways:
  A. Relapsed or refractory disease, defined as progression after two or more lines of systemic therapy (which may or
  may not include therapy supported by haematopoietic stem cell transplant), including *all* of the following:
    1. Anti-CD20 monoclonal antibody, such as rituximab; **AND**
    2. An anthracycline-containing chemotherapy regimen; **AND**
  B. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;

  OR
  C. Refractory disease to first-line chemotherapy or relapse within 12 months of first-line chemotherapy including all of the following:
    1. Anti-CD20 monoclonal antibody, such as rituximab; **AND**
    2. An anthracycline-containing chemotherapy regimen; **AND**
  D. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1;

  OR
  E. Refractory disease to first-line chemotherapy or relapse after first-line chemotherapy including *all* of the following:
    1. Anti-CD20 monoclonal antibody, such as rituximab; **AND**
    2. An anthracycline-containing chemotherapy regimen; **AND**
  F. Are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; **AND**
  G. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2;

  OR
  H. For relapsed or refractory follicular lymphoma, defined as progression after two or more lines of systemic therapy, including all of the following:
    1. Anti-CD20 monoclonal antibody, such as rituximab; **AND**
    2. An alkylating agent; **AND**
  I. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;

  OR
  J. For relapsed or refractory mantle cell lymphoma, defined as progression after two or more lines of systemic therapy, including all of the following:
    1. Bruton tyrosine kinase inhibitor (BTK); **AND**
    2. An alkylating agent; **AND**
    3. An anti-CD20 monoclonal antibody, such as rituximab; **AND**
  K. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1;

AND

IV. Individual has adequate bone marrow reserve; **AND**
V. If individual has a history of an allogeneic stem cell transplant, there are no current signs of active graft versus host disease (GVHD); **AND**
VI. Individual has not received prior treatment with CAR T-cell therapy or other genetically modified T-cell therapy; **AND**
VII. Individual is using as a one-time, single administration treatment.

Breyanzi (lisocabtagene maraleucel) for **B-cell lymphomas** may not be approved for the following:

I. Repeat administration; **OR**
II. Diagnosis of primary central nervous system lymphoma; **OR**
III. Cardiac ejection fraction (EF) less than 40%, or other clinically significant cardiac disease; **OR**
IV. Using in combination with other chemotherapy agents (not including the use of lymphodepleting chemotherapy prior to infusion); **OR**
V. History or presence of CNS disorders such as epilepsy/seizure disorder, paresis, aphasia, stroke, cerebral edema, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or pyschosis; **OR**
VI. If prescribed in combination with other CAR T-cell immunotherapy (e.g. Abecma, Carvykti, Kymriah, Tecartus, Yescarta); **OR**
VII. Individual has active GVHD; **OR**
VIII. Active or latent hepatitis B, active hepatitis C, or other active, uncontrolled infection; **OR**
IX. When the above criteria are not met, and for all other indications.

Requests for Breyanzi (lisocabtagene maraleucel) for **Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)** may be approved if the following criteria are met (Label, NCCN 2A):

I. Individual is 18 years of age or older; **AND**
II. Individual has a diagnosis of Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma (CLL or SLL); **AND**
III. Individual has relapsed or refractory disease, defined as progression after two or more lines of systemic therapy, including all of the following:
    A. BTK inhibitor (e.g. ibrutinib acalabrutinib); **AND**
    B. BCL-2 inhibitor (e.g. venetoclax); **AND**
IV. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; **AND**
V. Individual has adequate bone marrow reserve; **AND**
VI. Individual is using as a one-time, single administration treatment.

Breyanzi (lisocabtagene maraleucel) for **Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL)** may not be approved for the following:

I. Repeat administration; **OR**
II. Diagnosis of primary central nervous system lymphoma; **OR**
III. Active or latent hepatitis B, active hepatitis C, or other active, uncontrolled infection; **OR**
IV. If prescribed in combination with other CAR T-cell immunotherapy (e.g. Abecma, Carvykti, Kymriah, Tecartus, Yescarta); **OR**
V. If individual received prior gene therapy; **OR**
VI. Individual has active GVHD; **OR**
VII. If individual has Richter transformation (RT); **OR**
VIII. When the above criteria are not met, and for all other indications.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS

Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose [Breyanzi]

ICD-10 Diagnosis

	All diagnosis pend (applies to NOC codes only)
C82.00-C82.99	Follicular lymphoma
C83.00-C83.09	Small cell B-cell lymphoma
C83.10-C83.19	Mantle cell lymphoma
C83.30	Diffuse large B-cell lymphoma, unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma, intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma, intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma, intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma, lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma, extranodal and solid organ sites
C83.90	Non-follicular (diffuse) lymphoma, unspecified
C83.91	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of head, face, and neck
C83.92	Non-follicular (diffuse) lymphoma, unspecified, intrathoracic lymph nodes
C83.93	Non-follicular (diffuse) lymphoma, unspecified, intra-abdominal lymph nodes
C83.94	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of axilla and upper limb
C83.95	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of inguinal region and lower limb
C83.96	Non-follicular (diffuse) lymphoma, unspecified, intrapelvic lymph nodes
C83.97	Non-follicular (diffuse) lymphoma, unspecified, spleen
C83.98	Non-follicular (diffuse) lymphoma, unspecified, lymph nodes of multiple sites
C83.99	Non-follicular (diffuse) lymphoma, unspecified, extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face, and neck

C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites
C85.80	Other specified types of non-Hodgkin lymphoma, unspecified site
C85.81	Other specified types of non-Hodgkin lymphoma, lymph nodes of head, face, and neck
C85.82	Other specified types of non-Hodgkin lymphoma, intrathoracic lymph nodes
C85.83	Other specified types of non-Hodgkin lymphoma, intra-abdominal lymph nodes
C85.84	Other specified types of non-Hodgkin lymphoma, lymph nodes of axilla and upper limb
C85.85	Other specified types of non-Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C85.86	Other specified types of non-Hodgkin lymphoma, intrapelvic lymph nodes
C85.87	Other specified types of non-Hodgkin lymphoma, spleen
C85.88	Other specified types of non-Hodgkin lymphoma, lymph nodes of multiple sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)
Z51.12	Encounter for antineoplastic immunotherapy

Document History

Revised: 06/10/2024
Document History:

- 06/10/2024 – Select Review: Add criteria for FDA approval in r/r Follicular Lymphoma and Mantle cell lymphoma. Add references. Coding Reviewed: Expanded ICD-10-CM code range to include C82.00-C82.99, added C83.10-C83.19.
- 05/17/2024 – Select Review: Add criteria for FDA approval in CLL/SLL. Coding Reviewed: Added ICD-10-CM C83.00-C83.09, C91.10-C91.12. Added (Effective 11/28/2022) ICD-10-CM D47.Z1.
- 11/19/2023 – Annual Review: Update criteria due to NCCN nomenclature updates—HIV related lymphomas instead of “AIDS”; Clarify criteria in RN V for “current’ signs of active graft versus host disease. Remove HIV from may not be approved criteria. Coding Reviewed: No changes.
- 11/28/2022 – Annual Review: Update criteria to include diagnoses with 2A recommendations from NCCN for AIDS related B cell lymphomas and monomorphic PTLD; Add criteria for history of allogeneic stem cell transplant; Add criteria for prior CAR -T cell therapy; Update may not be approved criteria for combination use with other CAR T- cell therapy and active GVHD individuals; Removed following criteria from may not be approved section: CrCL, history of allogeneic stem cell transplant, and history of CAR T therapy. Coding Reviewed: No changes.
- 08/19/2022 – Select Review: Update criteria with FDA indications for use in refractory disease to first line chemotherapy. Coding Reviewed: Removed ICD-10-CM C82.40-C82.59, C83.30-C83.99, C85.20-C85.29. Added ICD-10-CM C83.90, C83.91, C83.92, C83.93, C83.94, C83.95, C83.96, C83.97, C83.98,C83.99, C85.10, C85.12, C85.13, C85.14, C85.15, C85.16, C85.17, C85.18, C85.19, C85.20, C85.21, C85.22, C85.23, C85.24, C85.25, C85.26, C85.27, C85.28, C85.29. Effective 10/1/2022- Added ICD-10-CM C82.40-C82.49, C83.30-C83.39, C85.80-C85.89.
- 11/19/2021 – Annual Review: No changes. Coding reviewed: No changes.
- 02/19/2021 – Annual Review: Add clinical criteria for Breyanzi (lisocabtagene maraleucel). Coding reviewed: Added HCPCS J3490, J3590, J9999. All diagnosis pend. Effective 7/1/2021 Added HCPCS

C9076. Added ICD-10-CM 82.40-C82.59, C83.30-C83.99, C85.20-C85.29, Z51.12. Removed HCPCS J9999. Effective 10/1/2021 Added Q2054. Removed C9076, J3490, J3590.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.