Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Lisocabtagene maraleucel (Breyanzi®)	MP-RX-FP-112-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drug

Service Description

This document addresses the use of Lisocabtagene maraleucel (Breyanzi®), a CD19-directed genetically modified autologous T cell immunotherapy approved by the Food and Drug Administration (FDA) for the treatment of certain 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.

Background Information

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

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.

Of note, Breyanzi's TRANSCEND study originally allowed individuals with an ECOG score of 2 to be enrolled, but the protocol was amended in 2017 (2 years after study initiation) to restrict to only ECOG of 0 to 1 for unknown reasons. A total of 4 patients (1% of study population) had ECOG of 2.

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. Due to these black box warnings, Breyanzi is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.

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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 house work, 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.

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Approved Indications

Lisocabtagene maraleucel (Breyanzi®) is approved by the FDA 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.

Other Uses

None

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
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	Description
	All diagnosis pend (applies to NOC codes only)
C82.40	Follicular lymphoma grade IIIb
C82.41	Follicular lymphoma grade IIIb, lymph nodes of head, face, and neck
C82.42	Follicular lymphoma grade IIIb, intrathoracic lymph nodes
C82.43	Follicular lymphoma grade IIIb, intra-abdominal lymph nodes
C82.44	Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb
C82.45	Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb
C82.46	Follicular lymphoma grade IIIb, intrapelvic lymph nodes
C82.47	Follicular lymphoma grade IIIb, spleen
C82.48	Follicular lymphoma grade IIIb, lymph nodes of multiple sites
C82.49	Follicular lymphoma grade IIIb, extranodal and solid organ sites

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ICD-10	Description
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

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ICD-10	Description
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
Z51.12	Encounter for antineoplastic immunotherapy

Medical Necessity Guidelines

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.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Lisocabtagene maraleucel (Breyanzi®)

A. Criteria For Initial Approval

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; **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 Grade 3B; **OR**
   - F. AIDS Related B-Cell Lymphomas (NCCN 2A); **OR**
   - G. 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;

AND

iv. Individual has adequate bone marrow reserve; **AND**

v. If individual has a history of an allogeneic stem cell transplant, there are no 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.

B. Criteria For Continuation of Therapy

i. Further treatment with Breyanzi will not be authorized since it is designated for a single-dose administration as per its indication.

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C. Authorization Duration

i. Initial Approval Duration: 3 months (1 dose only, tocilizumab (Actemra) will be approved if requested)
ii. Reauthorization Approval Duration: Not applicable

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

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, human immunodeficiency virus (HIV) positive, or other active, uncontrolled infection; **OR**
ix. When the above criteria are not met, and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

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B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Use	Recommended Dosing Schedule
Relapsed or Refractory LBCL After One Line of Therapy	A single dose of Breyanzi contains 90 to 110 × 106 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.
Relapsed or Refractory LBCL After Two or More Lines of Therapy	A single dose of BREYANZI contains 50 to 110 × 106 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.

Additional Information

- Breyanzi is designated for autologous administration via intravenous infusion solely within a certified healthcare setting.
- **Pretreatment**: Breyanzi should be initiated 2 days after completing lymphodepleting chemotherapy regimen with cyclophosphamide 300 mg/m^2/day intravenously (IV) and fludarabine 30 mg/m^2/day IV for 3 days. Breyanzi administration should be delayed in patients who experience unresolved serious adverse events after preceding chemotherapies; active infections or active graft-versus-host disease (GVHD).
- **Premedication** should include acetaminophen (650 mg orally) and diphenhydramine (25 to 50 mg orally, or another H1-antihistamine) approximately 30 to 60 minutes before infusion of Breyanzi. Prophylactic use of dexamethasone or other systemic corticosteroids should be avoided, as the use may interfere with the activity of Breyanzi.
- **Post-medication**: Tocilizumab plays an important role in the treatment of patients receiving CAR T-cell therapy such as Breyanzi. It manages and mitigates cytokine release syndrome (CRS), which can occur after CAR T-cell infusion. Tocilizumab should be available to the patient prior to infusion and during the recovery period.

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Reference Information

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11. NCCN Clinical Practice Guidelines in Oncology™. © 2022 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed October 16, 2022.
    a. B-Cell Lymphomas. V5.2022. Revised July 12, 2022.
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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.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Adopted from Elevance	N/A	12/22/2023

Revised: 11/28/2023