CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Lisocabtagene Maraleucel (Breyanzi®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Lisocabtagene Maraleucel (Breyanzi®)

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.

Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Lisocabtagene Maraleucel (Breyanzi): Discussion

Non-Hodgkin's lymphomas (NHL) are the seventh leading site of new cancer cases, accounting for 4%-5% of new cancer cases and 3% to 4% of cancer-related deaths. Diffuse large B-Cell lymphoma (DLBCL) accounts for 32% and follicular lymphoma (FL) accounts for 17% of lymphomas. [1]

High-Grade B-cell Lymphomas are LBCL's with translocations of MYC and BCL2 or BCL6 as detected by FISH or standard cytogenetics. These are known as "double hit" lymphomas or if all three are rearranged, they are referred to as "triple hit" lymphomas. These HGBL often present with poor prognostic parameters, such as elevated LDH, bone marrow and CNS involvement, and a high international prognostic index (IPI) score. [1]

Follicular lymphoma treatment is based on grades. Follicular lymphoma grade 3B receives the same treatment as DLBCL. [1]

Post-transplant lymphoproliferative disorders (PTLD) are a heterogeneous group of lymphomas that occur after a solid organ transplant (SOT) or an allogeneic hematopoietic cell transplant (HCT) and are related to immunosuppression and the Epstein-Barr virus (EBV). PTLD following SOT are of recipient origin in many of the patients, and often involve the grafted organ, whereas PTLD following an allogeneic HCT are usually of donor origin. [1]
Primary mediastinal B-cell lymphomas are a distinct subtype of NHL, which can be histologically indistinguishable from DLBCL, and tends to occur in young adults with a median age of 35 years with a slight female predominance. PMBL arises from thymic B-cells with initial locoregional spread to supraclavicular, cervical, hilar nodes and into the mediastinum and lung. PMBL accounts for 2% of mature B-cell lymphomas in children and adolescents. [1, 2]

Lisocabtagene maraleucel is a CD19-directed genetically modified autologous T cell immunotherapy. T-cells are collected from the patient and re-engineered in the laboratory to produce proteins on their surface called chimeric antigen receptors, or CARs. The CARs recognize and bind to specific proteins, or antigens, on the surface of cancer cells. After the revamped T cells are expanded into the millions in the laboratory, they are infused back into

the patient. Lisocabtagene maraleucel is 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 one of the following:

1. Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy
2. 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
3. Relapsed or refractory disease after two or more prior lines of systemic therapy. The NCCN also allows for an indication for pediatric patients with primary mediastinal Large B-Cell Lymphoma. At this time, the indication for lisocabtagene maraleucel in the pediatric setting has been extrapolated from adult clinical trials. [2,3,4]

For patients receiving lisocabtagene maraleucel in the third line plus setting, 46% experienced CRS with 4.1% experiencing grade 3 or higher. The median onset to CRS was 5 days with a median time to resolution of 5 days. The most common clinical manifestations of CRS (>10%) included fever (94%), hypotension (42%), tachycardia (28%), chills (23%), hypoxia (16%), and headache (12%). [4]

Due to the potential complications of CAR-T therapy including Cytokine Release Syndrome (CRS), and neurologic deficits, all staff involved in prescribing, dispensing, or administering lisocabtagene maraleucel are trained per the Risk Evaluation and Mitigation Strategy (REMS) program requirements. [4,5]

In the second line setting, there were 12% of patients that experienced any grade neurological events with 4% having grade 3. The median time to onset for neurologic events was 11 days and the median time to resolution was 6 days.

In the third line or greater setting, neurological events occurred in 30% of patients, with 9% experiencing grade 3 and 1% experiencing grade 4 events. The median time to onset of neurological events was 9 days with a median time to resolution of 11 days. The most common neurological events of any grade were encephalopathy (reported in 57 patients, 21% of patients overall, and 71% of patients with neurological events), tremors, and aphasia (each reported in 26 patients, 10% of patients overall, and 33% of patients with neurological events) and delirium (reported in 16 patients, 6% of patients overall and 20% of patients with neurological events). [6,7]

Lisocabtagene Maraleucel: Definitions

- **Cytokine release syndrome (CRS) -** A life-threatening complication of lisocabtagene maraleucel therapy. In the patient's receiving lisocabtagene maraleucel in the second-line setting, CRS occurred in 45% of LBCL patients, including grade 3 CRS in 1.3% of patients. The median time to onset of CRS was 4 days and the median time to resolution was 4 days.
- **Food and drug administration (FDA)** - The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **International prognostic index (IPI) -** A tool used in NHL to help identify specific groups of patients who are more or less likely to be cured with standard therapy. Scores are based on the patient's age, the stage of disease, serum LDH level, ECOG PS, and the number of extranodal sites. Points are given per each risk factor the patient has and the total will show the patient's risk factor to be low, low-intermediate, high-intermediate, and high.
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.
- **Risk Evaluation and Mitigation Strategy (REMS)** - A REMS program is a drug safety program to manage known or potential risks associated with a drug(s) and is required by the US Food and Drug Administration (FDA) to ensure that the benefits of a drug outweigh its risks. Lisocabtagene maraleucel is only available under a restricted program called Lisocabtagene maraleucel REMS because of the serious risks of CRS and neurological toxicities. The program ensures that hospitals and their associated clinic(s) that dispense lisocabtagene maraleucel are specially certified and have on-site immediate access to a minimum of two doses of tocilizumab. Those involved in the program must successfully complete the knowledge assessment and submit it to the REMS Program. [2,3]

Lisocabtagene Maraleucel: Policy

Lisocabtagene Maraleucel will be considered for coverage when the following criteria are met:

Large B-Cell Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. A diagnosis of large B-cell lymphoma including one of the following:
   a) Diffuse large B-Cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma)
   b) High-grade B-cell lymphoma
   c) Primary mediastinal large B-cell lymphoma; OR
4. Follicular lymphoma grade 3B; AND
5. Has been treated with first-line therapy containing an anthracycline and rituximab (or another CD20-targeted agent); AND
6. Meets one of the following:
   a) Relapsed or refractory disease after two or more lines of systemic therapy
   b) Refractory disease to first-line chemoimmunotherapy (primary refractory) or relapse within 12 months of first-line chemoimmunotherapy
   c) Refractory disease to first-line chemoimmunotherapy (primary refractory) or relapse after first-line chemoimmunotherapy and ineligible for hematopoietic cell transplant (HCT) due to comorbidities or age; AND
7. Eastern cooperative oncology group (ECOG) performance status of 0 or 1; AND
8. Does not have any of the following:
   a) Primary central nervous system (CNS) lymphoma
   b) Prior CAR-T cell treatment; AND
9. Has been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV); AND
10. Healthcare facility/provider has enrolled in the lisocabtagene maraleucel REMS program; AND
11. A lymphodepleting regimen is started after confirmation of lisocabtagene maraleucel availability, consisting of cyclophosphamide and fludarabine at the physician's discretion

Post-Transplant Lymphoproliferative Disorders

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Diagnosis of relapsed/refractory monomorphic post-transplant lymphoproliferative disorder (PTLD-B-cell type) as one of the following:
   a) Second-line therapy for relapsed or refractory disease >12 months after completion of first-line therapy if no intention to proceed to transplant

b) Additional therapy for relapsed or refractory disease >12 months after completion of initial treatment with chemoimmunotherapy if partial response following second-line chemoimmunotherapy
c) Additional therapy for primary refractory disease (partial response, no response, or progression) or relapsed disease <12 months after completion of first-line therapy
d) Treatment of disease in second relapse or greater if partial response, no response, or progressive disease following therapy for relapsed or refractory disease; AND

4. Eastern cooperative oncology group (ECOG) performance status of 0 or 1; AND
5. Does not have any of the following:
   a) Primary central nervous system (CNS) lymphoma.
   b) Prior CAR-T cell treatment; AND
6. Has been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV); AND
7. Healthcare facility/provider has enrolled in the lisocabtagene maraleucel REMS program; AND
8. A lymphodepleting regimen is started after confirmation of lisocabtagene maraleucel availability, consisting of cyclophosphamide and fludarabine at the physician's discretion

Pediatric Primary Mediastinal Lymphoma:

1. Less than or equal to 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Receiving this therapy as consolidation/additional therapy if a partial response is achieved after therapy for relapsed or refractory disease (after use of ≥ 2 prior chemoimmunotherapy regimens [2]; AND
4. Has been treated with first-line therapy containing an anthracycline and rituximab (or another CD20-targeted agent); AND
5. An Eastern cooperative oncology group (ECOG) performance status of 0 or 1; AND
6. Does NOT have any of the following:
7. Primary central nervous system (CNS) lymphoma; OR
8. Prior CAR-T cell treatment; AND
9. Screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to the collection of cells; AND
10. Healthcare facility/provider has enrolled in the lisocabtagene maraleucel REMS program; AND
11. A lymphodepleting regimen is started after confirmation of lisocabtagene maraleucel availability, consisting of cyclophosphamide and fludarabine at the physician's discretion

Dosage:

1. For the second line-a single dose of 90-110 x 10^6 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.
2. For third-line or greater- a single dose of 50-110 x 10^6 CAR-positive viable T cells (consisting of 1:1 CAR-positive viable T cells of the CD8 and CD4 components), with each component supplied

For reauthorization:

Lisocabtagene maraleucel will not be reauthorized for continued therapy.

Note:

Coverage of lisocabtagene maraleucel will be provided for FDA-approved indications or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation or when all criteria are met.

Lisocabtagene maraleucel: References

1. National Comprehensive Cancer Network Guidelines. B-Cell Lymphomas (Version 3.2023). www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed May 15, 2023.
2. National Comprehensive Cancer Network Guidelines. Pediatric Aggressive Mature B-Cell Lymphomas (Version 1.2023). www.nccn.org/professional/physician_gls/pdf/ped_b-cell.pdf. Accessed May 15, 2023.
3. CAR T Cells: Engineering Patients' Immune Cells to Treat Their Cancers. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells. Accessed April 20, 2023.
4. Lisocabtagene maraleucel (Breyanzi) Package Insert. Package Insert - BREYANZI (fda.gov). Accessed May 15, 2023.
5. Risk Evaluation and Mitigation Strategy (REMS). https://www.breyanzirems.com/. Accessed May 15, 2023.
6. Kamdar et al, Lancet 399:2294-08;2022. https://pubmed.ncbi.nlm.nih.gov/35717989/. Accessed May 15, 2023.
7. Abramson et al, Lancet 396:839-52;2020. https://pubmed.ncbi.nlm.nih.gov/32888407/. Accessed May 15, 2023.

Lisocabtagene Maraleucel: Coding (CPT®, ICD 10, and HCPCS) *

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment. CPT codes are available through the AMA.

CODE	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
0540T	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous
0537T	Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day

0538T	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)
0539T	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration
XW033N7	Introduction of lisocabtagene maraleucel immunotherapy into peripheral vein, percutaneous approach, new technology group 7
XW043N7	Introduction of lisocabtagene maraleucel immunotherapy into central vein, percutaneous approach, New Technology Group 7
0871	Cell Collection with CPT code 0537T
0872	Specialized Biologic Processing and Storage, Prior to Transport with CPT code 0538T
0873	Storage and Processing after Receipt of Cells from Manufacturer with CPT code 0539T
0874	Infusion of Modified Cells with CPT code 0540T
0891	Special Processed Drugs -- FDA Approved Cell Therapy with HCPCS codes Q2041, Q2042, C9073 (replaced with Q2053 April 1, 2021), C9076 (replaced with Q2054 October 1, 2021), C9081 (replaced with Q2055 January 1, 2022) or C9399

Lisocabtagene Maraleucel: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	5/2/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	6/20/2023
6	Revision Changes:	