Blue Cross Blue Shield Blue Care Network of Michigan

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Effective Date: 10/03/2024

Breyanzi® (lisocabtagene maraleucel)

HCPCS: Q2054

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. FDA approved indications
   b. FDA approved age
   c. Prescribed by on in consultation with an oncologist
   d. Diagnosis of relapsed or refactory non-Hodgkin's lymphoma
      i. Treatment of patients with relapsed or refractory Non-Hodgkin's lymphoma of the following subtypes:
         1. Diffuse large B-cell lymphoma (DLBCL)
         2. Primary mediastinal B-cell lymphoma (PMBCL)
         3. Follicular lymphoma, grade 3B
      ii. Received ≥ 2 lines of chemotherapy, including rituximab and anthracycline
      OR
      iii. Refractory disease or relapse within 12 months of first-line anti-CD20 and anthracycline therapy
      OR
      iv. Refractory disease to first-line chemoimmunotherapy or relapse after first-line therapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age
      v. Patients must meet all of the following
         1. ECOG performance status of 0 - 2
         2. Creatinine clearance greater than 30 mL/min
         3. Alanine aminotransferase less than 5 times the upper limit of normal
         4. Left ventricular ejection fraction greater than 40%
         5. No known active CNS involvement by primary malignancy (secondary CNS involvement is allowed)
         6. No history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy
         7. No infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
         8. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
         9. No presence of graft-vs-host disease (GVHD)

10. No myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
11. No thromboembolic events within 6 months
12. No pulmonary disease requiring oxygen dependence or pulmonary disease such as idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening
13. No clinically significant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

e. Diagnosis of relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
    i. Must have received at least 2 prior lines of therapy including all of the following
        1. A Bruton tyrosine kinase (BTK) inhibitor
        2. A B-cell lymphoma 2 (BCL-2) inhibitor
    ii. Patients must meet all of the following
        1. ECOG performance status of 0 - 2
        2. No known active central nervous system malignancy
        3. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
        4. No infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
        5. Creatinine clearance greater than 30 mL/min
        6. Alanine aminotransferase less than 5 times upper limit of normal
        7. Left ventricular ejection fraction greater than 40%
        8. Platelets greater than 50,000/mm^3
        9. No second malignancies in addition to CLL or SLL if the second malignancy has required therapy in the last 2 years or is not in complete remission
        10. No myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
        11. No thromboembolic events within 6 months
        12. No pulmonary disease requiring oxygen dependence or pulmonary disease such as idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening
        13. No clinically significant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

f. Diagnosis of relapsed or refractory follicular lymphoma (FL)
    i. Subjects must have received at least 2 prior lines of therapy including an anti-CD20 monoclonal antibody and an alkylating agent
    ii. Must have measurable disease
    iii. Patient must meet all of the following:
        1. No prior allogeneic HSCT
        2. No known active central nervous system malignancy
        3. ECOG performance status 0 - 2
        4. No transformed FL
        5. No histological grade 3b FL
        6. Creatinine clearance greater than 30 mL/min
        7. Hepatic transaminases less than 5 times the upper limit of normal
        8. Cardiac ejection fraction greater than 40%
        9. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
        10. No infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy

11. No myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
12. No thromboembolic events within 6 months
13. No pulmonary disease requiring oxygen dependence or pulmonary disease such as idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening
14. No clinically significant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis

g. Diagnosis of relapsed or refactory mantle cell lymphoma (MCL)
    i. Subjects must have received at least two prior line of therapy including all the following:
        1. An anthracycline or bendamustine-containing chemotherapy
        2. An anti-CD20 monoclonal antibody therapy
        3. A Bruton's tyrosine kinase (BTK) inhibitor
    ii. Must have 1 measurable lesion
    iii. Patient must meet all of the following:
        1. No known active central nervous system malignancy
        2. ECOG performance status 0 - 2
        3. Creatinine clearance greater than 30 mL/min
        4. Hepatic transaminases less than 5 times the upper limit of normal
        5. Cardiac ejection fraction greater than 40%
        6. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
        7. No infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
        8. No myocardial infarction, cardiac angioplasty or stenting, unstable angina, or New York Heart Association Class II or greater congestive heart failure events within 6 months
        9. No thromboembolic events within 6 months
        10. No pulmonary disease requiring oxygen dependence or pulmonary disease such as idiopathic pulmonary fibrosis, organizing pneumonia (eg, bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis per chest computed tomography (CT) scan at screening
        11. No clinically significant CNS pathology such as epilepsy, seizure, paresis, aphasia, stroke, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, organic brain syndrome, or psychosis
h. Have not received prior treatment with any CAR-T therapy despite indication or any other genetically-modified T-cell therapy or are being considered for treatment with any other genetically-modified T-cell therapy
i. Only to be administered at certified bone marrow/stem cell transplant centers
j. Trial and failure, intolerance, or a contraindication to the preferred products as listed in the BCBSM/BCN utilization management medical drug list
k. The requesting physician attests to providing clinical outcome information within the appropriate provider portal as requested by BCBSM
l. If new diagnoses are FDA approved, coverage will be determined based on the FDA approved indication on a case by case basis until fully evaluated by the BCBSM Pharmacy and Therapeutics Committee

B. Quantity Limitations, Authorization Period and Renewal Criteria
    a. Quantity Limits: Align with FDA recommended dosing
    b. Authorization Period: 3 months with the allowance of only one dose per lifetime
    c. Renewal Criteria: Not applicable as no further authorization will be provided

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

- CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

- Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

- Breyanzi is indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, 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. Breyanzi is not indicated for the treatment of patients with primary central nervous system lymphoma. Breyanzi is also 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; adult patients with relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy; and adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a BTK inhibitor.

- Safety and efficacy as third-line therapy were established in the TRANSCEND trial, an open-label, multicenter, single-arm study of 268 patients with relapsed or refractory large B-cell Non-Hodgkin's lymphoma. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after at least 2 lines of systemic therapy or after allogeneic HSCT. For patients who received previous CD19-targeted therapy, CD19-positive lymphoma confirmed on a biopsy had to be confirmed since completing the prior CD19-targeted therapy. Patients were excluded from the study if they had an ECOG performance status of greater than 2, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, left ventricular ejection fraction (LVEF) less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, had active infection, or the presence of graft-vs-host disease. The primary endpoints were complete response (CR) rate and duration of response (DOR). Seventy-three percent of patients achieved a response (95% CI: 67% - 80%), including 54% who experienced CR (95% CI: 47% - 61%) and 19% who achieved a partial response (PR; 95% CI: 14% - 26%). Median duration of response was 16.7 months in all responders (95% CI: 5.3 – not reached (NR)). For patients who achieved a CR, median duration of response was not reached (95% CI: 16.7 – NR). For patients achieving a PR, median duration of response was 1.4 months (95% CI: 1.1 – 2.2). Of 104 patients treated with Breyanzi who achieved a CR, 65% had remission lasting at least six months and 62% had remission lasting at least nine months.

- Safety and efficacy as second-line therapy were established in the TRANSFORM trial, a randomized, open-label, parallel-group, multicenter study of 184 patients with relapsed or refractory large B-cell Non-Hodgkin's lymphoma. Subjects must have been treated with an anthracycline and rituximab (or other CD20-targeted agent) and have relapsed or refractory disease after first-line therapy. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 45 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. The primary endpoint was event free survival (EFS). Breyanzi significantly improved median EFS compared with standard therapy (10.1 months vs. 2.3 months; HR = 0.34; p-value < 0.0001) and also significantly increased median progression free survival (PFS) (14.8 months vs. 5.7 months; HR = 0.4; p-value = 0.0001). Sixty-six percent of patients assigned Breyanzi achieved complete response to therapy compared with 39% of patients assigned standard treatment (p-value < 0.0001).

- Safety and efficacy for use in CLL or SLL were established in the TRANSCEND-CLL 004, a phase 1/2, open-label, multicenter study of 65 patients with relapsed or refractory CLL or SLL who had received at least 2 prior lines of therapy including a BTK inhibitor and a BCL-2 inhibitor. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. Of the evaluable patients, 45% and 20% achieved overall and complete responses, respectively. Of 13 MRD-evaluable patients, 100% and 92% achieved undetectable MRD in blood and marrow, respectively.

- Safety and efficacy for use in FL were established in the TRANSCEND-FL trial, a phase II, open-label, multicenter, single-arm study of 94 patients with relapsed or refractory FL following at least 2 prior lines of therapy including an anti-CD20 monoclonal antibody and an alkylating agent. Patients must have had measurable disease. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. The primary endpoint was overall response rate (ORR). The ORR was 95.7% (95% CI: 89.5–98.8). The CR rate was 73.4% (95% CI: 63.3–82.0). The median DOR was not reached after a median follow-up of 16.8 months.

- Safety and efficacy for use in MCL were established in the TRANSCEND-MCL trial, a phase II, open-label, multicenter, single-arm study of 68 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. Patients must have had measurable disease. Patients were excluded from the study if they had an ECOG performance status of greater than 1, a creatinine clearance less than 30 mL/min, alanine aminotransferase greater than 5 times the upper limit of normal, LVEF less than 40%, active CNS involvement by primary malignancy, history of another primary malignancy that has not been in remission for at least 2 years prior to consideration of CAR-T therapy, or had active infection. The primary endpoint was ORR. The ORR was 85.3% (95% CI: 74.6, 92.7) and 67.6% (95% CI: 55.2, 78.5) achieved a CR. The median DOR was 13.3 months (95% CI: 6.0, 23.3) with a median follow-up of 22.2 months (95% CI: 16.7, 22.8).

- Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

- A provider portal platform is used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

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<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>2.0</td><td>Effective Date: 10/03/2024</td><td>Updated criteria under CLL and SLL indication to read no central nervous system involvement of the malignancy and no second malignancies in addition to CLL or SLL if the second malignancy has required therapy in the last 3 years or is not in complete remission</td></tr>
<tr><td>1.9</td><td>Effective Date: 06/06/2024</td><td>Updated to include new indications for use in relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), follicular lymphoma (FL), and mantle cell lymphoma (MCL)</td></tr>
<tr><td>1.8</td><td>Effective Date: 02/08/2024</td><td>Updated to add preliminary criteria for use in relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)</td></tr>
<tr><td>1.7</td><td>Effective Date: 06/08/2023</td><td>Updated to require physicians provide clinical outcomes data using the Audaire Health platform</td></tr>
<tr><td>1.6</td><td>Effective Date: 08/04/2022</td><td>Updated to align criteria across all CAR-T policies and include new indication for use as second-line therapy in DLBCL</td></tr>
<tr><td>1.5</td><td>Effective Date: 06/09/2022</td><td>Updated to add preliminary criteria for use as second-line therapy in DLBCL</td></tr>
<tr><td>1.4</td><td>Effective Date: 04/14/2022</td><td>Updated to remove CD19 requirement as NCCN guidelines state CAR-T can work without being positive for CD19 disease</td></tr>
<tr><td>1.3</td><td>Effective Date: 08/12/2021</td><td>New policy - this policy replaces previously approved criteria that was embedded in Chimeric Antigen Receptor-T Cell Class policy which will be retired</td></tr>
<tr><td>1.2</td><td>Effective Date: 03/15/2021</td><td>UM medical management system update for BCBS
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.1</td><td>Effective Date: 03/08/2021</td><td>UM medical management system update for BCN
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.0</td><td>Effective Date: 02/11/2021</td><td>UM medical management system update for BCNA and MAPPO
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>No</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
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** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*