Medicare Advantage Medical Benefit Drug Policy

BlueCross BlueShield Nebraska

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Effective Date: 06/08/2023

Yescarta™ (axicabtagene ciloleucel)

HCPCS: Q2041

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 age
   b. Prescribed by or in consultation with an oncologist
   c. 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, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (TFL)
      i. Subjects must have received adequate prior therapy including at a minimum:
         1. Anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20-negative and
         2. An anthracycline containing chemotherapy regimen
         3. For subjects with transformed FL must have received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL
      ii. 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. Absolute lymphocyte count greater than 100/µL
         5. Creatinine clearance greater than 30 mL/min
         6. Hepatic transaminases less than 5 times the upper limit of normal
         7. Cardiac ejection fraction greater than 40%
         8. No infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
         9. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
         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

d. Treatment of adult patients with relapsed or refractory follicular lymphoma (FL)
   i. Subjects must have received at least 2 prior lines of therapy one of which is an anti-CD20 monoclonal antibody combined with 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

e. Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy
   i. Subjects must have received adequate prior therapy with an anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20-negative and an anthracycline containing chemotherapy regimen
   ii. Patient must meet all of the following:
      1. No prior allogeneic HSCT
      2. No known or suspected central nervous system involvement
      3. ECOG performance status of 0 - 2
      4. Absolute lymphocyte count greater than 100/µL
      5. Creatinine clearance greater than 30 mL/min
      6. Hepatic transaminases less than 5 times the upper limit of normal
      7. Cardiac ejection fraction greater than 40%
      8. No HIV infection; hepatitis B or C virus infection permitted only if viral load undetectable
      9. No infection that is uncontrolled or requires IV or long-term oral antimicrobial therapy
      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. 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
g. Only to be administered at certified bone marrow/stem cell transplant centers
h. Trial and failure, intolerance, or a contraindication to the preferred products as listed in the BCBSNE Part B drugs prior authorization list
i. 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 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

[a] Relapsed disease defined as complete remission to first-line therapy followed by biopsy-proven relapse ≤ 12 months of first-line therapy

[b] Refractory disease is defined as no complete remission to first-line therapy: progressive disease (PD) as best response to first-line therapy; stable disease (SD) as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP); or partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy.

***Note: Coverage 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.

- Yescarta 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 not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for the treatment of patients with primary central nervous system lymphoma. Yescarta is also indicated for adult patients with relapsed or refractory follicular lymphoma after two or more lines of systemic therapy.

- Efficacy was established in a single-arm, open-label, multicenter trial of 111 adult patients with relapsed or refractory aggressive B-cell non-Hodgkin lymphoma. Of 111 patients who underwent leukapheresis, 101 received Yescarta. One patient did not receive the product due to manufacturing failure and 9 others were not treated due to progressive disease or serious adverse reactions. Yescarta was administered as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T-cells/kg. The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously given on the fifth, fourth, and third day before Yescarta. Patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/μL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection were excluded. Subjects had previously received an anti-CD20 monoclonal antibody containing-regimen and an anthracycline-containing chemotherapy. Patients with transformed FL had received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to DLBCL. Primary endpoints were complete remission rate and duration of response. The median time to response was 0.9 months (range: 0.8 to 6.2 months). Of the 52 patients who achieved CR, 14 initially had stable disease (7 patients) or PR (7 patients), with a median time to improvement of 2.1 months (range: 1.6 to 5.3 months).

- Safety and efficacy for use in FL and MZL were established in the ZUMA-5 trial, an ongoing single-arm, open-label, multicenter phase 2 study of 104 adult patients with relapsed/refractory indolent NHL who had received up to 2 prior lines of therapy, including an anti-CD20 monoclonal antibody combined with an alkylating agent. Of the 104 patients, 84 had follicular lymphoma and 20 patients had marginal zone lymphoma and were required to have measurable disease. Patients were excluded if they had prior allogeneic HSCT, any history of central nervous system disease, ECOG performance status of 2 or greater, transformed FL, histological grade 3b FL, inadequate renal, hepatic, or cardiac function, or active serious infection. The primary endpoint is the objective response rate to therapy and key secondary endpoints include duration of response, progression-free survival (PFS), overall survival (OS), and incidence of adverse events. After a median follow-up of 17.5 months, the objective response rate was 92% with 76% of patients reaching a complete response. When broken down by exact indication, 94% (n = 84) of patients with relapsed/refractory FL had an objective response including 80% achieving a complete response. Of patients with relapsed/refractory MZL (n=20), 85% had an objective response with 60% achieving a complete response. At the data cutoff, 62% of all treated patients had ongoing responses. Median duration of response (DOR), progression-free survival (PFS) and overall survival (OS) were not reached.

- Safety and efficacy for use as second-line therapy in relapsed or refractory DLBCL is being established in the ZUMA-7 trial, an ongoing phase 3, randomized, open-label, multicenter study of 359 patients with replased/refractory DLBCL who had received one prior line of therapy that included an anti-CD20 monoclonal antibody combined with an anthracycline agent. Patients with prior allogeneic HSCT, any history of central nervous system lymphoma, ECOG performance status of 2 or greater, absolute lymphocyte count less than 100/μL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the upper limit of normal, cardiac ejection fraction less than 50%, or active serious infection were excluded. Relapsed disease was defined as complete remission to first-line therapy followed by biopsy-proven relapse ≤ 12 months of first-line therapy. Refractory disease was defined as no complete remission to first-line therapy: progressive disease (PD) as best response to first-line therapy; stable disease (SD) as best response after at least 4 cycles of first-line therapy (eg, 4 cycles of R-CHOP); or partial response (PR) as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤ 12 months of therapy. The primary endpoint is event-free survival (EFS) defined as time from randomization to disease progression, start of new lymphoma therapy, or death. ZUMA-7 met its primary EFS endpoint demonstrating statistically significant and clinically meaningful improvement in efficacy with Yescarta vs second-line standard of care.

- While use of Yescarta has not been established in patients with a creatinine clearance of less than 60 mL/minute, other CAR-T therapies have been studied in subjects with a creatinine clearance of 30 mL/minute. The National Institute of Health/National Cancer Institute Common Terminology Criteria of Adverse Events (CTCAE) classify grade 2 chronic kidney disease as a creatinine clearance of 30 – 59 mL/minute. As the classification system uses 30 mL/minute as a cutoff for grade 2 disease and data from other CAR-T therapies support their use in these patients, Yescarta should be able to be tolerated in this population. As there is no data to support administration of CAR-T at levels lower than 30 ml/minute, therapy should not be given in patients not meeting the 30 mL/minute threshold.

- While use of Yescarta has not been established in patients with an alanine aminotransferase of greater than 2.5 times the upper limit of normal (ULN), other CAR-T therapies have been studied in subjects with an alanine aminotransferase of up to 5 times the ULN and the CTCAE recommendations have set 5 times the ULN as the cutoff for grade 2 adverse reactions. As the classification system uses 5 times the ULN and other CAR-T therapies have data supporting use in this patient population, Yescarta should be tolerated in these patients as well. As there is no data to support administration of CAR-T at levels higher than 5 times the ULN, therapy should not be given to patients not meeting that threshold.

- The CTCAE recommendations set the grade 2 cutoff for left ventricular ejection fraction (LVEF) at 40%. While Yescarta has only been studied in patients with a LVEF greater than or equal to 50%, there is data from other CAR-T therapies to support use in those with a LVEF of 40% of greater. Therefore, Yescarta should be tolerated in these patients as well. There is no data supporting use at LVEF levels less than 40%.

References:

1. Yescarta [prescribing information]. Santa Monica, CA: Kite Pharma, Inc.; November 2022.
2. LaRussa A. Chimeric antigen receptor (CAR) t-cell therapy. 10 Sept. 2015. Available at: www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy. Access on August 3, 2017.
3. National Comprehensive Cancer Network. B-cell lymphomas (Version 2.2023). 2023 Feb 8. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed on April 10, 2023.
4. Lee DW et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10; 124 (2): 188 - 195.
5. Jacobson CA, Chavez JC, Sehgal AR, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2021 Dec 8; S1470-2045.
6. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large b-cell lymphoma. NEJM. 2022 Feb 17; 386: 640 – 654.
7. U.S. Department of Health and Human Services. Common terminology criteria for adverse events (Version 5.0). 2017 Nov 27. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed on July 8, 2022.

Policy History		
#	Date	Change Description
1.4	Effective Date: 06/08/2023	Annual review
1.3	Effective Date: 08/04/2022	Updated to align criteria across all CAR-T policies
1.2	Effective Date: 06/09/2022	Updated to include new indication allowing for use second-line in relapsed/refractory large B-cell lymphoma
1.1	Effective Date: 02/10/2022	Updated to include preliminary criteria for use as second-line therapy for DLBCL and remove the CD19 positive requirement
1.0	Effective Date: 08/12/2021	New policy

** 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.*