CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Axicabtagene Ciloleucel (Yescarta®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

Please note the following:

Axicabtagene Ciloleucel (Yescarta®)

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.

Axicabtagene Ciloleucel: 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% of lymphomas, follicular lymphoma accounts for 17%, and marginal zone lymphomas (MZL) accounts for 8%. [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]

Axicabtagene ciloleucel 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. Once reinfused back into the patient, the CAR-T cells will continue to multiply in the patient's body and, with guidance from their engineered receptor, recognize and kill any cancer cells that harbor the target antigen on their surfaces. Axicabtagene ciloleucel is indicated by the Food and Drug Administration (FDA) for the treatment of:

1. Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy; AND
2. 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, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma; AND
3. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy (accelerated approval based on response rate).[2,3]

Due to potential complications of CAR-T therapy including Cytokine Release Syndrome (CRS), and neurologic deficits, all staff involved in prescribing, dispensing, or administering

axicabtagene ciloleucel and/or brexucabtagene autoleucel are trained per the Risk Evaluation and Mitigation Strategy (REMS) program requirements. [2,4]

Axicabtagene Ciloleucel: Definitions

- **Cytokine release syndrome (CRS) -** A life-threatening complication of axicabtagene ciloleucel therapy. CRS occurred in 90% of patients with non-Hodgkin lymphoma (NHL) receiving axicabtagene ciloleucel, including over or equal to grade 3 CRS in 9%. CRS occurred in 93% of patients with LBCL, including ≥ 9% grade 3 CRS. CRS occurred in 84 % of patients with indolent non-Hodgkin lymphoma (iNHL), including ≥ 8 % grade 3 CRS. The most common clinical manifestations of CRS include pyrexia (85%), hypotension (40%), tachycardia (32%), chills (22%), hypoxia (20%), headache (15%) and fatigue (12%). [2,4]
- **Food and Drug Administration (FDA)-** The FDA is responsible for protecting 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.
- **National Comprehensive Cancer Network (NCCN)-** An alliance of 32 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.
- **Neurologic Toxicities -** Can be severe and life-threatening. These can occur in combination with CRS. The most frequent manifestations of axicabtagene ciloleucel-associated neurotoxicity include encephalopathy (50%), headache (43%), tremors (29%), dizziness (21%), aphasia (17%), delirium (15%) and insomnia (10%). The median onset of neurotoxicity for patients with large B-cell lymphoma (LBCL) was 4-5 days and lasted between 15-17 days and the median onset of those with FL (follicular lymphoma) was 6 days and lasted for a median duration of 16 days. [2,4]
- **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. Axicabtagene ciloleucel and/or brexucabtagene autoleucel are only available through this restricted program. The program ensures that hospitals and their associated clinic(s) that dispense axicabtagene ciloleucel are specially certified and have on-site, immediate access to a minimum of 2 doses of tocilizumab. The program also ensures that those who prescribe, dispense, or administer axicabtagene ciloleucel are aware of how to manage the risks of CRS and neurologic toxicities. Those involved in the program must successfully complete the knowledge assessment and submit it to the REMS Program. [2,4]

Axicabtagene Ciloleucel: Policy

Axicabtagene Ciloleucel 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. Diagnosis of large B-cell lymphoma, including diffuse large B-Cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma; AND
4. Disease is refractory or relapsed, defined as one of the following:
    a) No response, partial response, disease progression, or relapse after two or more lines of systemic therapy, including both:
        i. An anti-CD20 monoclonal antibody (e.g., rituximab) unless the tumor is CD20-negative
        ii. A chemotherapy regimen that contains an anthracycline
    b) Relapsed after autologous hematopoietic stem cell transplantation (HSCT)
    c) Primary refractory disease (incomplete response to first-line chemoimmunotherapy, including at least an anti-CD20 monoclonal antibody unless the tumor is CD20-negative and a chemotherapy regimen that contains an anthracycline)
    d) Relapsed within 12 months (complete remission following the first line chemoimmunotherapy that includes at least an anti-CD20 monoclonal antibody unless the tumor is CD20-negative and a chemotherapy regimen that contains an anthracycline, followed by relapse); AND
5. An Eastern cooperative oncology group (ECOG) performance status of 0 or 1; AND
6. None of the following exists:
    a) Prior allogeneic HSCT
    b) History or presence of primary central nervous system (CNS) lymphoma
    c) Prior CAR-T therapy; AND
7. Screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to collection of cells (negative results must be submitted); AND
8. Healthcare facility/provider has enrolled in the axicabtagene ciloleucel REMS program; AND
9. Weight is documented for dose calculation

Follicular Lymphoma:

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Diagnosis of relapsed or refractory follicular lymphoma; AND
4. Measurable disease after 2 or more lines of systemic therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent; AND
5. An Eastern cooperative oncology group (ECOG) performance status of 0 or 1; AND
6. None of the following exists:
    a) Prior allogeneic HSCT
    b) History or presence of primary central nervous system (CNS) lymphoma
    c) Prior CAR-T therapy; AND
7. Screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to collection of cells (negative results must be submitted); AND
8. Healthcare facility/provider has enrolled in the axicabtagene ciloleucel and brexucabtagene autoleucel (Tecartus) REMS program; AND
9. Weight is documented for dose calculation

Extranodal Marginal Zone Lymphoma on Non-Gastric Sites (Noncutaneous) and Extranodal Marginal Zone Lymphoma of the Stomach

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Diagnosis of relapsed, refractory, or progressive extranodal marginal zone lymphoma of non-gastric sites (noncutaneous) or extranodal marginal zone lymphoma of the stomach; AND
4. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; AND
5. None of the following exists:
    a) Prior allogeneic HSCT
    b) History or presence of primary central nervous system (CNS) lymphoma
    c) Prior CAR-T therapy; AND
6. Screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to collection of cells (negative results must be submitted); AND
7. Healthcare facility/provider has enrolled in the axicabtagene ciloleucel REMS program; AND
8. Weight is documented for dose calculation

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 post-transplant lymphoproliferative disorder (PTLD) as one of the following:

   a) Additional therapy for relapsed or refractory disease > 12 months after completion of initial treatment with chemoimmunotherapy if partial response following second line chemoimmunotherapy.
   b) Additional therapy for primary refractory disease (partial response, no response or progression) or relapsed disease < 12 months after completion of initial treatment with chemoimmunotherapy.
   c) 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. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; AND
5. None of the following exists:
   a) History or presence of primary central nervous system (CNS) lymphoma
   b) Prior CAR-T therapy; AND
6. Screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to collection of cells (negative results must be submitted); AND
7. Healthcare facility/provider has enrolled in the axicabtagene ciloleucel REMS program; AND
8. Weight is documented for dose calculation; AND

Nodal Marginal Zone Lymphoma and Splenic Marginal Zone Lymphoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Has a diagnosis of one of the following:
   a) Nodal marginal zone lymphoma and third-line and subsequent therapy for partial response, no response, relapsed, or progressive disease
   b) Splenic marginal zone lymphoma and third line and subsequent therapy for disease recurrence
4. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; AND
5. None of the following exists:
   d) Prior allogeneic HSCT
   e) History or presence of primary central nervous system (CNS) lymphoma
   f) Prior CAR-T therapy; AND
6. Screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) prior to collection of cells (negative results must be submitted); AND
7. Healthcare facility/provider has enrolled in the axicabtagene ciloleucel REMS program; AND
8. Weight is documented for dose calculation

Dosage:

1. A lymphodepleting regimen is started after confirmation of axicabtagene ciloleucel availability, consisting of cyclophosphamide 500 mg/m2 IV and fludarabine 30 mg/m2 IV on the fifth, fourth, and third day before infusion of axicabtagene ciloleucel.
2. Dosage allowed/Quantity limit: 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells.

For reauthorization:

Axicabtagene ciloleucel is a one-time dose and will not be renewed.

Note: Coverage of axicabtagene ciloleucel 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.

Axicabtagene ciloleucel: References

1. National Comprehensive Cancer Network Guidelines. B-Cell Lymphoma (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed April 20, 2023.
2. Package Insert - YESCARTA (fda.gov). https://www.fda.gov/media/108377/download. Accessed April 20, 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. Risk Evaluation and Mitigation Strategy (REMS). https://www.yescartatecartusrems.com/. Accessed April 20, 2023.
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 2022; 23:91-103.
6. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med 2022; 386:640-654.
7. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med 2017; 377:2531-2544.

Axicabtagene Ciloleucel: 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
0540T	CPT code for hospital outpatient setting along with drug code Q2041
0537T	(collection/handling) (Medicare will reject these codes on an outpatient claim, or they may be included in the charge reported for the biological)
0538T	(Preparation for transport) (Medicare will reject these codes on an outpatient claim, or they may be included in the charge reported for the biological)
0539T	(Receipt and preparation) (Medicare will reject these codes on an outpatient claim, or they may be included in the charge reported for the biological)
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.
C82.30	Follicular Lymphoma grade IIIa, unspecified site
C82.37	Follicular Lymphoma grade IIIa, spleen
C82.40	Follicular Lymphoma grade IIIb, unspecified site
C82.47	Follicular Lymphoma grade IIIb, spleen
C85.10	Unspecified B-Cell lymphoma, unspecified site
C85.20-C85.29	Primary Mediastinal Large B-Cell lymphoma
C83.30-C83.39	DLBCL codes

Q2041	Axicabtagene ciloleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
XW033H7	Yescarta: Introduction of axicabtagene ciloleucel immunotherapy into peripheral vein, percutaneous approach, new technology group 7
XW043H7	Yescarta: Introduction of axicabtagene ciloleucel immunotherapy into central vein, percutaneous approach, new technology group 7

Axicabtagene Ciloleucel: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	5/23/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	6/7/2023
6	Revision Changes:	