MEDICAL COVERAGE POLICY	
SERVICE:	**Axicabtagene ciloleucel (Yescarta®)**
Policy Number:	**278**
Effective Date:	**1/1/2025**
Last Review:	**10/14/2024**
Next Review:	**10/14/2025**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Axicabtagene ciloleucel (Yescarta®)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to Medicare NCD 110.24 Chimeric Antigen Receptor (CAR) T-cell Therapy

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

Baylor Scott & White Health Plan (BSWHP) may consider axicabtagene ciloleucel (Yescarta®) medically necessary for treatment of large B-cell lymphoma or classic follicular lymphoma **when ALL of the following universal criteria are met as well as criteria specific to each indication below:**

Universal Criteria Applied to All Requests

1. Member is ≥ 18 years old; **AND**
2. Member diagnosed by a hematologist or oncologist; **AND**
3. Axicabtagene ciloleucel will be used as monotherapy; **AND**
4. Dose and frequency should be consistent with FDA labeling or NCCN; **AND**
5. Member is eligible for apheresis; **AND**
6. Member has or will receive lymphodepleting chemotherapy (e.g., fludarabine and cyclophosphamide) before infusion of axicabtagene ciloleucel; **AND**
7. Provider attests all REMS program requirements are met; **AND**
8. Member has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; **AND**
9. Member has documentation of CD-19 tumor expression; **AND**
10. Member has NOT received prior treatment with CD-19 targeted CAR-T cell therapy; **AND**
11. If the member has received prior treatment with anti-CD19 therapy the member's repeat biopsy indicated CD-19 positive disease; **AND**
12. Member does NOT have any of the following conditions:
    a. Primary central nervous system (CNS) lymphoma

b. Active hepatitis B (HBs AG-positive), active hepatitis C, HIV infection, or uncontrolled infection
c. History of CNS disorders (ex. seizure disorder, cerebrovascular ischemia)
d. Active inflammatory disorder requiring systemic immunosuppression
e. Richter transformation
f. Active graft versus host disease (GVHD)
g. Allogeneic hematopoietic stem-cell transplantation in the preceding 84 days before leukapheresis
h. Unmanaged venous thrombosis or embolism
i. Pregnant

Indication Specific Criteria

Large B-cell Lymphoma (LBCL) specific criteria:

1. Member meets all universal criteria; **AND**
2. Member has a diagnosis of large B-cell lymphoma [i.e., diffuse large B-cell lymphoma (DBLCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma for which member has received chemotherapy]; **AND**
3. Member has one of the following**:**
   a. Refractory (partial response, no response, or progression) to first-line chemoimmunotherapy
   b. Relapsed from complete remission within 12 months of first-line chemoimmunotherapy
   c. Received two or more lines of systemic therapy with both an anthracycline chemotherapy regimen and anti-CD20 monoclonal antibody, unless tumor is CD-20 negative, AND has relapsed or refractory disease defined as one of the following:
      i. Progressive disease or stable disease relapsing in less than or equal to 6 months
      ii. Disease progression or recurrence less than or equal to 12 months after prior autologous stem cell transplant (ASCT)
      iii. If salvage therapy is given post-ASCT, member did not have response to, or relapsed after, the last line of therapy

   AND
4. If the member has DLBCL arising from follicular lymphoma then the member has received an anthracycline-based regimen, unless contraindicated

Follicular Lymphoma (FL) specific criteria:

1. Member meets all universal criteria; **AND**
2. Member has a diagnosis of follicular lymphoma; **AND**
3. Member has relapsed or refractory disease defined as progressive disease or stable disease relapsing within 12 months; **AND**
4. Member received two or more prior lines of systemic therapy with both an anti-CD20 monoclonal antibody and an alkylating agent

Only ONE dose per lifetime is medically necessary.

BSWHP considers axicabtagene ciloleucel (Yescarta®) for the treatment of all other indications to be experimental, investigational, and/or unproven.

All requests will be reviewed by both a clinical pharmacist and a medical director.

BACKGROUND:

Chimeric antigen receptor (CAR) T cells and genetically engineered T-cell receptor (TCR T) cells are manufactured by collecting lymphocytes from a patient or donor and modifying them using gene transfer techniques. Viral vectors are introduced that express cell receptors that are highly specific for tumor antigens. CAR T and TCR T cells are then infused back into the patient, where they direct a targeted immune response to cancerous tissue. CAR T cells express a hybrid receptor with an extracellular single-chain antibody fragment, a transmembrane domain, and at least 1 intracellular signaling domain. CAR T cells are most often used to treat hematological malignancies, and a common target is B-cell cluster of differentiation antigen 19 (CD19).

A study from Memorial Sloan Kettering Cancer Center looked at long-term data in a cohort of 53 adults with relapsed/refractory B-cell ALL. The median follow-up was 29 months (range: 1-65), the median event-free survival among the 53 treated patients was 6.1 months and the median overall survival was 12.9 months. Complete remission was observed in 83% of patients.

In a 2016 comprehensive review, Holtzinger et al. (2016) list over 100 ongoing clinical trials evaluating CAR T cells with a variety of targets for a variety of indications. Most of the trials are underway in the United States or Canada, and about a quarter of the trials are underway in China. They also allude to 7 completed phase I trials on CAR T cells for hematological malignancy. The authors conclude that more research is needed to identify ideal CAR T cell targets, receptor designs, and lymphodepletion regimens; control toxic effects like cytokine release syndrome (CRS); and evaluate the use of CAR T cells with HSCT.

Axicabtagene ciloleucel (Yescarta®) is an autologous CAR T-cell therapy, a novel type of immunotherapy in which a patient's own genetically altered immune cells are used to attack cancer cells.

The U. S. Food and Drug Administration (FDA) approved the Biologics License Application (BLA) for axicabtagene ciloleucel on October 18, 2017 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, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. This drug label contains the same boxed warning stating that axicabtagene ciloleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

The pivotal trial ZUMA that lead to approval was a phase 2 trial with 111 patients. Among the 111 patients who were enrolled, axicabtagene ciloleucel was successfully manufactured for 110 (99%) and administered to 101 (91%). The objective response rate was 82%, and the complete response rate was

54%.with a median follow-up of 15.4 months, 42% of the patients continued to have a response, with 40% continuing to have a complete response. The overall rate of survival at 18 months was 52%. Grade 3 or higher CRS and neurologic events occurred in 13% and 28% of the patients, respectively. Three of the patients died during treatment.

In March 2022, axicabtagene ciloleucel was approved for the treatment of adult patients with large B-cell lymphoma (LBCL) that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy based on the phase 3 ZUMA-7 trial. ZUMA-7 was a randomized, open-label, multicenter study of 359 patients with LBCL who had not yet received treatment for relapsed or refractory lymphoma and were potential candidates for autologous hematopoietic stem cell transplantation. Patients were randomized 1:1 to receive axicabtagene ciloleucel plus conditioning chemotherapy (n = 180) or standard of care (SOC) of salvage chemotherapy followed by consolidation high-dose therapy (HDT)-autologous stem cell transplant (ASCT) with platinum-based chemoimmunotherapy (n = 179). The estimated 18-month event free survival (EFS) rate was 41.5% (95% CI, 34.2, 48.6) with axicabtagene ciloleucel vs 17.0% (95% CI, 11.8, 23.0) with SOC.

In March 2021, the FDA approved axicabtagene ciloleucel for the treatment of adult patients with relapsed or refractory follicular lymphoma from the ZUMA-5 trial. ZUMA-5 was a single-arm, open-label, multicenter trial that enrolled 146 patients with either relapsed or refractory follicular lymphoma and marginal zone lymphoma who had previously received 2 or more lines of systemic therapy, including treatment with an anti-CD20 monoclonal antibody and an alkylating agent. Axicabtagene ciloleucel had an overall response rate of 91% of patients with relapsed/refractory follicular lymphoma (n = 81), 60% of patients who achieved a complete remission, and 74% of patients had a continued remission at 18 months.

National Comprehensive Cancer Network (NCCN) gives axicabtagene ciloleucel for subsequent therapy for transformed Follicular Lymphoma, diffuse large B-cell lymphoma, AIDs-related B-cell lymphomas, & Posttransplant Lymphoproliferative Disease a recommendation category of 2A.

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	36511 Therapeutic apheresis; for white blood cells
HCPCS Codes:	Q2041 - Yescarta (Axicabtagene ciloleucel)
ICD10 codes:	C82.00 - C82.99 Follicular lymphoma C83.30 - C83.39 Diffuse large B-cell lymphoma C85.20 - C85.29 Mediastinal (thymic) large B-cell lymphoma C85.80 - C85.89 Other specified types of non-Hodgkin lymphoma

ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	10/22/2020	New policy
Update	11/19/2020	Added criteria for prescriber and dosing
Update	04/22/2021	Added Medicaid statement
Update	05/27/2021	Removed Oncology Analytics line, added apheresis criteria, reformatted criteria
Update	07/22/2021	Added clinician reviewer criteria
Update	06/23/2022	Added new indications, NCD information
Updated	10/27/2022	Removed language with CMS LCD since NCD applies. Removed Texas Mandate HB1584 language from main policy section as the policy is compliant. Minor formatting update.
Reviewed	10/09/2023	Applied new layout and format.
Updated	10/14/2024	Reformatted with Universal and Specific criteria, Updated universal criteria to align exclusion criteria when applicable across CAR-T therapies

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

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Note:
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

RightCare STAR Medicaid is offered through Scott and White Health Plan in the Central Texas Medicaid Rural Service Area (MRSA); FirstCare STAR is offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs; and FirstCare CHIP is offered through FirstCare in the Lubbock Service Area.