MEDICAL COVERAGE POLICY	
SERVICE:	**Axicabtagene ciloleucel (Yescarta®)**
Policy Number:	**278**
Effective Date:	**1/1/2024**
Last Review:	**10/09/2023**
Next Review:	**10/09/2024**

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.

BSWHP may consider axicabtagene ciloleucel (Yescarta®) medically necessary for treatment of large B-cell lymphoma when the following criteria are met:

1. The 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**
2. The member is ≥ 18 years of age; **AND**
3. Member diagnosed by a hematologist or oncologist; **AND**
4. One-time, single administration treatment**; AND**
5. The member will be using axicabtagene ciloleucel at a certified treatment center; **AND**
6. The member has relapsed or refractory disease with one of the following**:**
   a. Refractory to first-line chemoimmunotherapy; **OR**
   b. Relapsed from complete remission within 12 months of first-line chemoimmunotherapy; **OR**
   c. Received two or more prior lines of systemic therapy with both an anthracycline containing 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:
      - Progressive disease or stable disease relapsing in less than or equal to 6 months; OR
      - Disease progression or recurrence less than or equal to 12 months after prior autologous stem cell transplant (ASCT);
      - If salvage therapy is given post-ASCT, member did not have response to, or relapsed after, the last line of therapy;

      AND

7. The member has or will receive lymphodepleting chemotherapy followed by infusion of axicabtagene within 2-14 days of completion of lymphodepleting chemo; **AND**
8. The member will NOT be treated with more than $2x10^8$ viable CAR-T cells; **AND**
9. Member does NOT have any of the following conditions:
   a. Active hepatitis B (HBs AG-positive) or active hepatitis C, or any uncontrolled infection
   b. Central nervous system (CNS) disease including seizures, cerebrovascular ischemia, or primary CNS lymphoma
   c. Grade 2-4 graft versus host disease if status-post allo-transplant
   d. On immunosuppression therapy for autoimmune disease/transplant
   e. ECOG performance status 2 or greater

   AND
10. Member has NOT previously been treated with CD-19 targeted therapy or prior CD-19 targeted CAR-T cell therapy; **AND**
11. Member has been assessed by a hematologist/oncologist to be an appropriate candidate for apheresis.

BSWHP may consider axicabtagene ciloleucel (Yescarta®) medically necessary for treatment of follicular lymphoma when the following criteria are met:

1. The member has a diagnosis of follicular lymphoma; **AND**
2. The member is ≥ 18 years of age; **AND**
3. Member diagnosed by a hematologist or oncologist; **AND**
4. One-time, single administration treatment**; AND**
5. The member will be using axicabtagene ciloleucel at a certified treatment center; **AND**
6. The member has relapsed or refractory disease defined as progressive disease or stable disease relapsing in less than 1 year **AND**
   a. Received two or more prior lines of systemic therapy with both an anti-CD20 monoclonal antibody and an alkylating agent

   AND
7. The member has or will receive lymphodepleting chemotherapy followed by infusion of axicabtagene within 2-14 days of completion of lymphodepleting chemo; **AND**
8. The member will NOT be treated with more than $2x10^8$ viable CAR-T cells; **AND**
9. Member does NOT have any of the following conditions:
   a. Active, uncontrolled infection including infection requiring intravenous antimicrobials, HIV, or active hepatitis B or hepatitis C
   b. History of CNS disease including seizures, cerebrovascular ischemia, or primary CNS lymphoma
   c. Transformed lymphoma or other aggressive lymphomas
   d. Prior allogeneic hematopoietic stem cell transplant (HSCT)
   e. ECOG performance status 2 or greater

   AND

10. Member has NOT previously been treated with CD-19 targeted therapy or prior CAR-T cell therapy; **AND**
11. Member has been assessed by a hematologist/oncologist to be an appropriate candidate for apheresis.

BSWHP considers repeat administration of axicabtagene experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers axicabtagene to be experimental and investigational for all other indications.

All requests will be reviewed by a clinical pharmacist and 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.

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.

1. Almåsbak H, Aarvak T, Vemuri MC. CAR T cell therapy: a game changer in cancer treatment. J Immunol Res. 2016;2016:5474602.
2. Brentjens RJ. Are chimeric antigen receptor T cells ready for prime time? Clin Adv Hematol Oncol. 2016;14(1):17-19.
3. Brudno JN, Somerville RP, Shi V, et al. Allogeneic T cells that express an anti-CD19 chimeric antigen receptor induce remissions of B-cell malignancies that progress after allogeneic hematopoietic stem-cell transplantation without causing graft-versus-host disease. J Clin Oncol. 2016;34(10):1112-1121.
4. Children's Hospital of Philadelphia (CHOP). What to Expect: CAR T-cell Therapy Process. 2017. Available at: http://www.chop.edu/centers-programs/cancer-immunotherapy-program/your-experience. Accessed August 8, 2017.
5. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. Crit Care Med. 2017;45(2):e124-e131.
6. Gardner RA, Finney O, Annesley C, et al. Intent-to-treat leukemia remission by CD19 CAR T cells of defined formulation and dose in children and young adults. Blood. 2017;129(25):3322-3331.

7. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-4190.
8. Harris DT, Kranz DM. Adoptive T cell therapies: a comparison of T cell receptors and chimeric antigen receptors. Trends Pharmacol Sci. 2016;37(3):220-230.
9. Hettle R, Corbett M, Hinde S, et al. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. Health Technol Assess. 2017;21(7):1-204.
10. Holzinger A, Barden M, Abken H. The growing world of CAR T cell trials: a systematic review. Cancer Immunol Immunother. 2016;65(12):1433-1450.
11. Ikeda H. T-cell adoptive immunotherapy using tumor-infiltrating T cells and genetically engineered TCR-T cells. Int Immunol. 2016;28(7):349-353.
12. Inman S. Juno Accelerates Development of JCAR017, Halts JCAR015. March 2, 2017. Available at: http://www.onclive.com/web-exclusives/juno-accelerates-development-of-jcar017-halts-jcar015. Accessed August 8, 2017.
13. 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(1):91-103. doi:10.1016/S1470-2045(21)00591-X
14. Kebriaei P, Singh H, Huls MH, et al. Phase I trials using Sleeping Beauty to generate CD19-specific CAR T cells. J Clin Invest. 2016;126(9):3363-3376.
15. Kochenderfer JN, Somerville RPT, Lu T, et al. Lymphoma remissions caused by anti-CD19 chimeric antigen receptor T cells are associated with high serum interleukin-15 levels. J Clin Oncol. 2017;35(16):1803-1813.
16. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385(9967):517-528.
17. Leukemia and Lymphoma Society (LLS). Chimeric Antigen Receptor (CAR) T-Cell Therapy. 2017. Available at: https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy.
18. Locke FL, Davila ML. Regulatory challenges and considerations for the clinical application of CAR-T cell anti-cancer therapy. Expert Opin Biol Ther. 2017;17(6):659-661.
19. 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(7):640-654. doi:10.1056/NEJMoa2116133
20. Locke FL, Neelapu SS, Bartlett NL, et al. Phase 1 results of ZUMA-1: a multicenter study of KTE-C19 anti-CD19 CAR T cell therapy in refractory aggressive lymphoma. Mol Ther. 2017;25(1):285-295.
21. Lymphoma Research Foundation (LRF). Diffuse Large B-Cell Lymphoma (DLBCL). 2016. Available at: http://www.lymphoma.org/site/pp.asp?c=bkLTKaOQLmK8E&b=6300153. Accessed August 8, 2017.
22. Martin A, Morgan E, Hijiya N. Relapsed or refractory pediatric acute lymphoblastic leukemia: current and emerging treatments. Paediatr Drugs. 2012;14(6):377-387.
23. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-1517.
24. Maus MV, Nikiforow S. The why, what, and how of the new fact standards for immune effector cells. J Immunother Cancer. 2017;5:36.
25. Pan J, Yang JF, Deng BP, et al. High efficacy and safety of low-dose CD19-directed CAR-T cell therapy in 51 refractory or relapsed B acute lymphoblastic leukemia patients. Leukemia. 2017. Epub ahead of print. May 15, 2017. Available at: http://www.nature.com/leu/journal/vaop/ncurrent/full/leu2017145a.html?foxtrotcallback=true. Accessed August 8, 2017.
26. Rapoport AP, Stadtmauer EA, Binder-Scholl GK, et al. NY-ESO-1-specific TCR-engineered T cells mediate sustained antigen-specific antitumor effects in myeloma. Nat Med. 2015;21(8):914-921.
27. Rose S. DLBCL responds well to anti-CD19 CAR therapy. Cancer Discov. 2017;7(3):241-242.
28. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125(1):22-32.

29. Turtle CJ, Hanafi LA, Berger C, et al. CD19 CAR-T cells of defined CD4+:CD8+ composition in adult B cell ALL patients. J Clin Invest. 2016a;126(6):2123-2138.
30. Turtle CJ, Hanafi LA, Berger C, et al. Immunotherapy of non-Hodgkin's lymphoma with a defined ratio of CD8+ and CD4+ CD19-specific chimeric antigen receptor-modified T cells. Sci Transl Med. 2016b;8(355):355ra116.
31. Turtle CJ, Hay KA, Hanafi LA, et al. Durable molecular remissions in chronic lymphocytic leukemia treated With CD19-specific chimeric antigen receptor-modified T cells after failure of ibrutinib. J Clin Oncol. 2017:JCO2017728519. Epub ahead of print. July 17, 2017. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.72.8519?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed&. Accessed August 8, 2017.
32. Ye B, Stary CM, Gao Q, et al. Genetically modified T-cell-based adoptive immunotherapy in hematological malignancies. J Immunol Res. 2017;2017:5210459.
33. Zhang T, Cao L, Xie J, et al. Efficiency of CD19 chimeric antigen receptor-modified T cells for treatment of B cell malignancies in phase I clinical trials: a meta-analysis. Oncotarget. 2015;6(32):33961-33971.
34. Locke FL, Neelapu SS, Bartlett NL, Siddiqi T, Chavez JC, Hosing CM, Ghobadi A, Budde LE, Bot A, Rossi JM, Jiang Y, Xue AX, Elias M, Aycock J, Wiezorek J, Go WY. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma. Mol Ther. 2017 Jan 4;25(1):285-295. doi: 10.1016/j.ymthe.2016.10.020. Epub 2017 Jan 4.
35. Locke FL, et. al. Phase 1 Results of ZUMA-1: A Multicenter Study of KTE-C19 Anti-CD19 CAR T Cell Therapy in Refractory Aggressive Lymphoma.
36. Zachary J. Roberts, Marc Better, Adrian Bot, Margo R. Roberts & Antoni Ribas (2017): Axicabtagene ciloleucel, a first-in-class CAR T cell therapy for aggressive NHL, Leukemia & Lymphoma, DOI: 10.1080/10428194.2017.1387905
37. Riviere I, et. al. Long-term follow-up of CD19 CAR therapy in Acute Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):449-459.
38. Neelapu SS, Locke FL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017;377:2531-2544

***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 plans are offered through Scott and White Health Plan in the Central Managed Care Service Area (MRSA) and STAR and CHIP plans are offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs.