MEDICAL COVERAGE POLICY SERVICE: Axicabtagene ciloleucel (Yescarta®)	
Policy Number:	**278**
Effective Date:	**01/01/2021**
Last Review:	**11/19/2020**
Next Review Date:	**11/19/2020**

Important note
Unless otherwise indicated, this policy will apply to all lines of business.
Even though this policy may indicate that a particular service or supply may be considered medically necessary and thus covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage (EOC) or Summary Plan Description (SPD) to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare-linked plan members, this policy will apply unless there are Medicare policies that provide differing coverage rules, in which case Medicare coverage rules supersede guidelines in this policy. Medicare-linked plan policies will only apply to benefits paid for under Medicare rules, and not to any other health benefit plan benefits. CMS's Coverage Issues Manual can be found on the CMS website. Similarly, for Medicaid-linked plans, the Texas Medicaid Provider Procedures Manual (TMPPM) supersedes coverage guidelines in this policy where applicable.

SERVICE: Adoptive Immunotherapy

PRIOR AUTHORIZATION: Required. This policy provides guidelines for medical review when that review is NOT performed by vendor Oncology Analytics.

POLICY: **For Medicare plans**, please refer to appropriate Medicare LCD (Local Coverage Determination). If there is no applicable LCD, use the criteria set forth below.

Axicabtagene ciloleucel (Yescarta®)

SWHP/FirstCare may consider axicabtagene (Yescarta®) medically necessary 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 at a certified treatment center.
6. The member has relapsed or refractory disease, **AND EITHER:**
   a. For members of Plans subject to Texas Mandate HB1584: the member has stage 4 advanced metastatic disease; **OR**
   b. 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;
7. The member has or will receive lymphodepleting chemotherapy followed by infusion of axicabtagene within 2-14 days of completion of lymphodepleting chemo.

8. The member will NOT be treated with more than $2x10^8$ viable CAR-T cells

Members with the following conditions are **NOT** eligible for treatment with axicabtagene:

- Active hepatitis B (HBs AG-positive) or active hepatitis C, or any uncontrolled infection
- CNS disease including primary CNS lymphoma
- Grade 2-4 graft versus host disease if status-post allo-transplant
- On immunosuppression therapy for autoimmune disease/transplant
- Has received prior CD-19 targeted therapy AND/OR prior CD-19 targeted CAR-T cell therapy

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

SWHP/FirstCare considers axicabtagene to be experimental and investigational for the following diagnoses secondary to paucity of safety and efficacy data (not all-inclusive list):

a. Adults and Pediatric acute lymphoblastic leukemia
b. Acute Myeloid Leukemia
c. Follicular Lymphoma
d. Non-Hodgkin's Lymphoma - indolent
e. Multiple myeloma
f. Mantle Cell Lymphoma
g. Primary central nervous system lymphoma.

OVERVIEW

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 (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.

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The U. S. Food and Drug Administration (FDA) approved the Biologics License Application (BLA) for axicabtagene 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 is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

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%.

The pivotal trial (ZUMA) that lead to approval was a phase 2 trial with 111 patients. Among the 111 patients who were enrolled, axicabtagene 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.

National Comprehensive Cancer Network (NCCN) gives axicabtagene 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:
CODES: 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
CPT Not Covered:	
HCPCS	Q2041 - Yescarta (Axicabtagene ciloleucel) S2107 Adoptive immunotherapy i.e., development of specific an-tumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment
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:	

CMS:

POLICY HISTORY:

Status	Date	Action
New	10/22/2020	New policy
Update	11/19/2020	Added criteria for prescriber and dosing

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. SWHP will continue to review clinical evidence related to this policy and may modify it at a later date 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 SWHP 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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