 **Approved Revision: Do Not Implement until 8/31/21**

## Axicabtagene Ciloleucel (Yescarta®)

**NDC CODE(S)** 71287-0119-XX YESCARTA PLASTIC BAG, INJECTION (KITE PHARMA, IN)

**DESCRIPTION**

Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare the product an individual's own T cells are harvested and genetically modified ex vivo by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains. The anti-CD19 CAR T cells are expanded and infused back into the individual.

Axicabtagene ciloleucel binds to CD19-expressing cancer cells and normal B cells. Studies demonstrated that following anti-CD19 CAR T cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signaling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

**POLICY**

- Axicabtagene ciloleucel for the treatment of the following is considered ***medically necessary*** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**
  - Large B-cell Lymphoma
  - Follicular Lymphoma
- Axicabtagene ciloleucel for the treatment of other conditions/diseases is considered ***investigational.***

**MEDICAL APPROPRIATENESS**

**INITIAL APPROVAL CRITERIA**

**Submission of medical records related to the medical necessity criteria is REQUIRED on all requests for authorizations. Records will be reviewed at the time of submission. Please provide documentation via direct upload through the PA web portal or by fax.**

- Patient does not have a clinically significant active systemic infection or inflammatory disorder; **AND**
- Patient has not received live vaccines within 6 weeks prior to the start of lymphodepleting chemotherapy, during axicabtagene ciloleucel treatment, and will not receive live vaccines until immune recovery following treatment; **AND**
- Patient has been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in accordance with clinical guidelines prior to collection of cells (leukapheresis); **AND**
- Prophylaxis for infection has been followed according to local guidelines; **AND**
- Healthcare facility has enrolled in the Yescarta and Tecartus REMS Program and training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities; **AND**
- Patient has not received prior CAR-T therapy; **AND**
- Patient has not received prior anti-CD19 therapy, (e.g., blinatumomab, etc.) OR patient previously received anti-CD19 therapy and re-biopsy indicates CD-19 positive disease; **AND**
- Used as single agent therapy (not applicable to lymphodepleting or additional chemotherapy while awaiting manufacture); **AND**
- Patient did not receive prior allogeneic hematopoietic stem cell transplantation (HSCT); **AND**
- Patient aged 18 years or greater; **AND**

- Patient has an ECOG performance status of 0-1; **AND**

**Large B-Cell Lymphoma**

- Patient does not have primary central nervous system lymphoma; **AND**
- Patient's disease is relapsed or refractory defined as a relapse within 1 year after autologous hematopoietic stem cell transplantation (HSCT) OR disease refractory to the most recent therapy; **AND**
  - Patient has Diffuse large B-cell lymphoma (DLBCL) as histologic transformation; **AND**
    - Patient received two or more prior lines of chemoimmunotherapy which must have included an anthracycline or anthracenedione-based regimen, unless contraindicated; **AND**
    - Patient had Follicular Lymphoma (FL) or Nodal Marginal Zone Lymphoma; **AND**
      - Patient received multiple lines of prior therapies for indolent or transformed disease; **OR**
    - Patient had Follicular Lymphoma (FL); **AND**
      - Patient received minimal or no chemotherapy prior to histologic transformation and had partial response, no response, or progressive disease after treatment; **OR**
  - Patient has Richter's transformation of CLL to DLBCL; **AND**
    - Patient received two or more prior lines of systemic therapy; **OR**
    - Used for treatment of disease that is in second or greater relapse; **OR**
  - Patient has AIDS-related diffuse large B-cell lymphoma, primary effusion lymphoma, DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), or high grade B-cell lymphoma, HHV8-positive diffuse large B-cell lymphoma, not otherwise specified, or monomorphic post-transplant lymphoproliferative disorder (B-cell type); **AND**
    - Used as additional therapy for patients with intention to proceed to transplant who have partial response following second-line therapy for relapsed or refractory disease; **OR**
    - Used for treatment of disease that is in second or greater relapse

**Follicular Lymphoma (FL)**

- Patient has relapsed or refractory grade 1-2 disease; **AND**
- Patient has received two or more prior lines of systemic therapy

**RENEWAL CRITERIA**

**Coverage cannot be renewed.**

**DOSAGE/ADMINISTRATION**

| INDICATION | DOSE |
|---|---|
| Large B-Cell Lymphoma and Follicular Lymphoma | **Lymphodepleting chemotherapy:**<br>• Administer cyclophosphamide 500 mg/m2 and fludarabine 30 mg/m2 intravenously on the fifth, fourth, and third day before infusion of Yescarta<br>**Yescarta Infusion:**<br>• Premedicate with 650 mg acetaminophen and 12.5 mg diphenhydramine 1 hour prior to infusion. Avoid prophylactic system corticosteroids which may interfere with Yescarta activity.<br>• Infuse the entire contents of the Yescarta bag within 30 minutes by either gravity or a peristaltic pump.<br>• Each single infusion bag of Yescarta contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. The target dose is 2 × 106 |

| | |
|---|---|
| | CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108 CAR-positive viable T cells.<br>**Monitoring:**<br>• Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities.<br>• Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion. |
| **For autologous use only. For intravenous use only.**<br>• Yescarta is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure.<br>• One treatment course consists of lymphodepleting chemotherapy followed by a single infusion of Yescarta.<br>• Confirm Yescarta availability prior to starting the lymphodepleting regimen. | |
| • Store infusion bag in the vapor phase of liquid nitrogen (less than or equal to minus 150°C). Thaw prior to infusion.<br>• In case of manufacturing failure, a second manufacturing may be attempted.<br>• Additional chemotherapy (not the lymphodepletion) may be necessary while the patient awaits the product.<br>• Ensure that 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period. | |

**LENGTH OF AUTHORIZATION**

Coverage will be provided for one treatment course (1 dose of Yescarta) and may not be renewed.

**DOSING LIMITS**

**Max Units (per dose and over time) [HCPCS Unit]:**

- 1 billable unit (1 infusion of up to 200 million autologous anti-CD19 CAR-positive viable T-cells)

**APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS**

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

**IMPORTANT REMINDER**

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

**ADDITIONAL INFORMATION**

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex

Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

**SOURCES**

1. Yescarta [package insert]. Santa Monica, CA; Kite Pharma, Inc., March 2021. Accessed March 2021.
2. 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 Jan 4;25(1):285-295.
3. Mejstrikova E, Hrusak O, Borowitz MJ, et al. CD19-negative relapse of pediatric B-cell precursor acute lymphoblastic leukemia following blinatumomab treatment. Blood Cancer J. 20177; 659. DOI 10.1038/s41408-017-0023-x
4. Ruella M, Maus MV. Catch me if you can: Leukemia Escape after CD19-Directed T Cell Immunotherapies. Computational and Structural Biotechnology Journal 14 (2016) 357–362.
5. Braig F, Brandt A, Goebeler M, et al. Resistance to anti-CD19/CD3 BiTE in acute lymphoblastic leukemia may be mediated by disrupted CD19 membrane trafficking. Blood; 129:1, 2017 Jan.
6. Majzner RG, Mackall CL. Tumor Antigen Escape from CAR T-cell Therapy. Cancer Discov 2018;8:1219-1226.
7. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) axicabtagene ciloleucel. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed March 2021.
8. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31-42. doi:10.1016/S1470-2045(18)30864-7.
9. Neelapu SS, Jacobson CA, Oluwole OO, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2020;135(23):2106-2109. doi:10.1182/blood.2019004162.
10. 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(26):2531-2544. doi: 10.1056/NEJMoa1707447.
11. Jacobson CA, Chavez JC, Sehgal AR, et al. Interim analysis of ZUMA-5: A phase II study of axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory indolent non-Hodgkin lymphoma (R/R iNHL). Journal of Clinical Oncology 2020 38:15_suppl, 8008-8008.
12. MICROMEDEX Healthcare Series. Drugdex Evaluations. (2021, March). *Axicabtagene ciloleucel*. Retrieved April 19, 2021 from MICROMEDEX Healthcare Series.

**EFFECTIVE DATE** 8/31/2021

ID_MRx