Yescarta® (axicabtagene ciloleucel)
(Intravenous)

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Document Number: IC-0454

Last Review Date: 12/01/2020
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I. Length of Authorization

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

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- 1 infusion bag

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

- 1 billable unit (1 infusion up to 200 million autologous anti-cd19 car -positive viable t-cells)

III. Initial Approval Criteria [1-10]

- 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.

Coverage is provided in the following conditions:

- 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**
- Patient does not have primary central nervous system lymphoma; **AND**

Large B-Cell Lymphoma † Φ

- 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 systemic therapy which must have included an anthracycline and anti-CD20 monoclonal antibody (unless tumor is CD20-negative); **AND**
        - Patient had Follicular Lymphoma (FL); **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 DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), or high grade B-cell lymphoma; **AND**
        - Patient received two or more prior lines of systemic therapy which must have included an anthracycline as well as an anti-CD20 monoclonal antibody (unless tumor is CD20-negative)

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendium Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria[1]

Coverage cannot be renewed.

V. Dosage/Administration [1]

Indication	Dose
Large B-Cell Lymphoma	<u>Lymphodepleting chemotherapy</u>: • Administer cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 intravenously on the fifth, fourth, and third day before infusion of Yescarta <u>Yescarta Infusion</u>: • 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. • Infuse the entire contents of the Yescarta bag within 30 minutes by either gravity or a peristaltic pump • 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 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum of 2×10^8 CAR-positive viable T cells. <u>Monitoring</u>: • Monitor patients at least daily for 7 days at the certified healthcare facility following infusion for signs and symptoms of CRS and neurologic toxicities. • 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. • Yescarta is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure • One treatment course consists of lymphodepleting chemotherapy followed by a single infusion of Yescarta. • 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. • In case of manufacturing failure, a second manufacturing may be attempted. • Additional chemotherapy (not the lymphodepletion) may be necessary while the patient awaits the product. • Ensure that 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period. • Yescarta contains human blood cells that are genetically modified with replication incompetent retroviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal.	

VI. Billing Code/Availability Information

<u>HCPCS Code</u>:

- Q2041 - Axicabtagene Ciloleucel, up to 200 million autologous anti-cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

- <u>NDC</u>:
  - Yescarta suspension for intravenous infusion; 1 infusion bag (68 mL): 71287-0119-xx

VII. References (STANDARD)

1. Yescarta [package insert]. Santa Monica, CA; Kite Pharma, Inc., July 2020. Accessed October 2020.

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, 2020. 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 October 2020.
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.

VIII. References (ENHANCED)

1e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) B-Cell Lymphomas, Version 4.2020. National Comprehensive Cancer Network, 2020. 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 NCCN Guidelines, go online to NCCN.org. Accessed October 2020.
2e. Schuster S, Bishop M, Tam C, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2019; 380:45-56.
3e. Magellan Health, Magellan Rx Management. Yescarta Clinical Literature Review Analysis. Last updated October 2020. Accessed October 2020.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C83.30	Diffuse large B-cell lymphoma unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma, unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes
C85.23	Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma, spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD , Local Coverage Article and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCA/LCD): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto Government Benefit Administrators, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate

Large B-Cell Lymphoma

Relapsed or Refractory Disease (Diffuse Large B-cell Lymphoma [DLBCL], Primary Mediastinal Large B-cell Lymphoma, High Grade B-cell Lymphoma, DLBCL Arising From Follicular Lymphoma)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Axicabtagene ciloleucel	2A	Yes (patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy)	Phase 2 (ZUMA-1), multicenter 2-year follow-up	N/A	ORR	Refractory disease or relapse within 1 year after auto-HCT; previously received an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy; for FL, received prior chemotherapy for FL and subsequently have	• Patients with refractory large B-cell lymphoma who received CAR T-cell therapy with axi-cel had an ORR of 82%, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events.

						chemorefractory disease after transformation to DLBCL; prior therapies ranged from 1-10 (77% refractory to ≥2 lines of therapy)	
Tisagenlecleucel	2A	Yes (DLBCL not otherwise specified [NOS], high grade B-cell lymphoma, DLBCL arising from follicular lymphoma [FL])	Phase 2 (JULIET), single-arm, open-label, multicenter	N/A	ORR	R/R DLBCL (after ≥ 2 lines of chemo, including rituximab and anthracycline, and were ineligible for or had relapsed following auto-HSCT)	• In relapsed or refractory diffuse large B-cell lymphoma in adults, high rates of durable responses were produced with the use of tisagenlecleucel (ORR 52% and 12-mon estimated relapse-free survival of 65%).
AIDS-related diffuse large B-cell lymphoma or HHV8-positive diffuse large B-cell lymphoma, not otherwise specified OR monomorphic post-transplant lymphoproliferative disorder							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**

Axicabtagene ciloleucel	2A	No	No clinical trial evidence to support use.				
Richter's transformation							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Axicabtagene ciloleucel	No	No	No clinical trial evidence to support use.				