Clinical Policy: Axicabtagene Ciloleucel (Yescarta)

Reference Number: LA.PHAR.362
Effective Date:
Last Review Date: 04.22 — **Coding Implications**
Line of Business: Medicaid — **Revision Log**

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Axicabtagene ciloleucel (Yescarta™) is a CD19-directed, genetically modified, autologous T cell immunotherapy.

FDA Approved Indication(s)

Yescarta is indicated for the treatment of adult patients with

- **Relapsed or refractory large B-cell lymphoma (LBCL):**
  - **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.**
  - **[Pending] Relapsed/refractory LBCL in the second-line setting**
  - **Limitation of use: Yescarta is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.***
- **Relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy**
  - **This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).**

Efficacy of Yescarta has not been established in patients with a history of or current CNS lymphoma (see Appendix D)

Policy/Criteria

Prior authorization is required. Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

All requests reviewed under this policy require medical director review.

It is the policy of Louisiana Healthcare Connections that Yescarta is medically necessary when the following criteria are met:

I. Initial Approval Criteria

A. Large B-Cell Lymphoma* (must meet all):

Only for initial treatment dose; subsequent doses will not be covered.

Criteria will mirror the clinical information from the prescribing information once FDA-approved

Commented [BJ1]: PI updated April 2021 with new indication.

Commented [ACE2R1]: Updated with current PI

1. **Diagnosis of one of the following LBCL (a–f);**
   a. **DLBCL;**
   b. **Primary Mediastinal Large B Cell Lymphoma (PMBCL); ;≠**
   c. **Transformed Follicular Lymphoma (TFL) to DLBCL;**
   d. **Transformed Nodal Marginal Zone lymphoma (MZL) to DLBCL;**
   e. **High-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) or high-grade B-cell lymphomas, not otherwise specified;**
   f. **Monomorphic post-transplant lymphoproliferative disorders (B-cell type);**
2. **Prescribed by or in consultation with an oncologist or hematologist;**
3. **Age ≥ 18 years;**
4. **Recent (within the last 30 days) absolute lymphocyte count (ALC) ≥ 100/µL;**
5. **Request is for one of the following (a or b):**
   a. **Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes rituximab* and one anthracycline-containing regimen (e.g., doxorubicin);**
   b. **Disease that is refractory (defined as no complete remission) to or has relapsed (defined as complete remission followed by biopsy-proven disease relapse) no more than 12 months after first-line chemoimmunotherapy that included an anti-CD20 monoclonal antibody (e.g., rituximab*) and anthracycline-containing regimen (e.g., doxorubicin); [Pre-emptive Indication]^≠**

   ^Pre-emptive indication: This is a P&T approved policy and should only be used after this indication is FDA approved. Off-label requests prior to FDA approval should not be reviewed/approved using these criteria.
   ****Prior authorization may be required for rituximab***

6. **Member does not have a history of or current CNS disease;**
7. **Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma®, Breyanzi®, Kymriah™, Tecartus®);**
8. **Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Kymriah, Tecartus);**
9. **Dose does not exceed 2 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells.≠**

Approval duration: 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) if requested at up to 800 mg per dose)*

B. Follicular Lymphoma* (must meet all):
****Only for initial treatment dose; subsequent doses will not be covered.***

1. **Diagnosis of FL grade 1, 2, or 3a;**
2. **Prescribed by or in consultation with an oncologist or hematologist;**
3. **Age ≥ 18 years;**
4. **Disease is relapsed/refractory after ≥ 2 lines of systemic therapy that includes a combination of an anti-CD20 monoclonal antibody (e.g., rituximab or Gazyva®) and an alkylating agent (e.g., bendamustine, cyclophosphamide, chlorambucil)*;**

Prior authorization may be required

5. **Member does not have a history of or current CNS disease;**
6. **Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Kymriah, Tecartus);**
7. **Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Kymriah, Tecartus);**
8. **Dose does not exceed a single administration of 2 x 10^8 chimeric antigen receptor (CAR)-positive viable T cells.**

Approval duration: 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) if requested at up to 800 mg per dose)*

C. Other diagnoses/indications

1. **Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.**

II. Continued Therapy

A. All Indications in Section I

1. **Continued therapy will not be authorized as Yescarta is indicated to be dosed one time only.**

Approval duration: Not applicable

B. Other diagnoses/indications

1. **Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): LA.PMN.53 for Medicaid.**

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policy –LA.PMN.53 for Medicaid, or evidence of coverage documents;

B. History of or current CNS disease.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALC: absolute lymphocyte count
CAR: chimeric antigen receptor
CNS: central nervous system
CRS: cytokine release syndrome
DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration
FL: follicular lymphoma
LBCL: large B-cell lymphoma
MZL: marginal zone lymphoma
TFL: transformed follicular lymphoma

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Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
First-Line Treatment Regimens		
RCHOP (Rituxan® (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (Rituxan® (rituximab), cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCDOP (Rituxan® (rituximab), cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	Varies	Varies
DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicine) + Rituxan® (rituximab)	Varies	Varies
RCEOP (Rituxan® (rituximab), cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies
RGCVP (Rituxan®, gemcitabine, cyclophosphamide, vincristine, prednisone)	Varies	Varies
Second-Line Treatment Regimens		
Bendeka® (bendamustine) ± Rituxan® (rituximab)	Varies	Varies
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± Rituxan® (rituximab)	Varies	Varies
CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± Rituxan® (rituximab)	Varies	Varies
DA-EPOCH ± Rituxan® (rituximab)	Varies	Varies
GDP (gemcitabine, dexamethasone, cisplatin) ± Rituxan® (rituximab)	Varies	Varies
gemcitabine, dexamethasone, carboplatin ± Rituxan® (rituximab)	Varies	Varies
GemOx (gemcitabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies
gemcitabine, vinorelbine ± Rituxan® (rituximab)	Varies	Varies
lenalidomide ± Rituxan® (rituximab)	Varies	Varies
Rituxan® (rituximab)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine) ± Rituxan® (rituximab)	Varies	Varies
DHAX (dexamethasone, cytarabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± Rituxan® (rituximab)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide) ± Rituxan® (rituximab)	Varies	Varies
MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± Rituxan® (rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
FL First-Line and Second-Line + Subsequent Treatment Regimens		
bendamustine + (Gazyva® (obinutuzumab) or rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + (Gazyva® (obinutuzumab) or rituximab)	Varies	Varies
CHOP + Gazyva® (obinutuzumab) or rituximab	Varies	Varies
CVP (cyclophosphamide, vincristine, prednisone) + Gazyva® (obinutuzumab)		
CVP + Gazyva® (obinutuzumab) or rituximab	Varies	Varies
rituximab ± (lenalidomide, chlorambucil, or cyclophosphamide)	Varies	Varies
rituximab	Varies	Varies
Gazyva® (obinutuzumab)	Varies	Varies
Zevalin® (ibritumomab tiuxetan)	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- **Contraindication(s): none reported**
- **Boxed warning(s): cytokine release syndrome (CRS), neurologic toxicities**

Appendix D: General Information

- **The ZUMA-1 trial included only patients that received prior anti-CD20 antibody therapy and an anthracycline-containing regimen. Patients with an ALC < 100/µL were excluded.**
- **The ZUMA-1 trial inclusion criteria required a MRI of the brain showing no evidence of CNS lymphoma. Patients with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases were excluded. For primary DLBCL of the CNS (i.e., primary CNS lymphoma), NCCN treatment guidelines for CNS cancers recommend a high-dose methotrexate induction based regimen or whole brain radiation therapy, which consolidation therapy with high-dose chemotherapy with stem cell rescue, high-dose cytarabine with or without etoposide, low dose whole brain radiation therapy, or continuation with monthly high-dose methotrexate-based regimen.**
- **Bennani et al. 2019 reported on the real-world experience of 17 patients treated with Yescarta who had a history of secondary CNS involvement or had active CNS disease at time of CAR-T infusion. Among the 15 patients who received a Yescarta infusion, 10 had resolution of CNS involvement, and 5 had persistent active CNS disease at the time of infusion. The best overall response rates (complete and partial responses) at 30-days between the non-CNS and CNS cohorts were 75% vs 59%**

respectively (p = 0.15). Best overall response rates at month 6 were 41% vs 31% respectively (p = 0.60).

- **CRS, including fatal or life-threatening reactions, occurred in patients receiving Yescarta. Do not administer Yescarta to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.**
- **Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving Yescarta, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with Yescarta. Provide supportive care and/or corticosteroids, as needed.**
- **Yescarta is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Yescarta REMS.**

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
LBCL, FL	Target dose: 2×10^6 CAR-positive viable T cells per kg body weight	2×10^8 CAR-positive viable T cells

VI. Product Availability

Single-dose unit infusion bag: frozen suspension of genetically modified autologous T-cells labeled for the specific recipient

VII. References

1. **Yescarta Prescribing information. Santa Monica, CA: Kite Pharma, Inc.; April 2021. Available at www.yescarta.com. Accessed October 19, 2021.**
2. **Data on File. Kite Pharma - Yescarta: Primary Results of the Pivotal ZUMA-1 Phase 2 Study. MRC-00038. October 2017.**
3. **National Comprehensive Cancer Network. B-cell Lymphomas Version 5.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed October 19, 2021.**
4. **National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed October 19, 2021.**
5. **National Comprehensive Cancer Network. Central Nervous System Cancers Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed October 19, 2021.**
6. **Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. NEJM 2017; 377: 2531-44.**
7. **Bennani NN, Maurer MJ, Nastoupil LJ, et al. Experience with Axicabtagene Ciloleucel (Axi-cel) in Patients with Secondary CNS Involvement: Results from the US Lymphoma CAR T Consortium. Blood (2019); 134 (Supplement_1): 763.**
8. **ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine (US). Identifier NCT03105336, A phase 2 multicenter study of axicabtagene ciloleucel in subjects with relapsed/refractory indolent non-hodgkin lymphoma (ZUMA-5); 25**

February 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03105336. Accessed October 19, 2021.
9. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2021 Dec 11. Epub ahead of print. PMID: 34891224.
10. ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine (US). Identifier NCT03391466, Efficacy of Axicabtagene Ciloleucel Compared to Standard of Care Therapy in Subjects With Relapsed/Refractory Diffuse Large B Cell Lymphoma (ZUMA-7); 14 October 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT03391466. Accessed December 22, 2021.

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
Q2041	Axicabtagene Ciloleucel, up to 200 million autologous anti-CD19 CAR positive viable T Cells, including leukapheresis and dose preparation procedures, per therapeutic dose

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy	04.22	

Important Reminder
This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate

of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. LHCC retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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