Clinical Policy: Axicabtagene Ciloleucel (Yescarta)

Reference Number: ERX.SPA.221
Effective Date: 12.01.17
Last Review Date: 05.21
Line of Business: Commercial, 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 LBCL, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
  - 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

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

Policy/Criteria

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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.*

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. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes Rituxan® and one anthracycline-containing regimen (e.g., doxorubicin);
   **Prior authorization may be required for Rituxan*
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., Kymriah™, Breyanzi®);

8. Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Kymriah, Breyanzi);
9. Dose does not exceed 2 x 10^8 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., Kymriah, Breyanzi);
7. Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Kymriah, Breyanzi);
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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 – ERX.PA.01 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	DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration	FL: follicular lymphoma
CAR: chimeric antigen receptor	LBCL: large B-cell lymphoma
CNS: central nervous system	MZL: marginal zone lymphoma
CRS: cytokine release syndrome	TFL: transformed follicular lymphoma

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
LBCL 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 (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone)	Varies	Varies
LBCL 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
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.
- 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.
- 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).
- 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.; February 2021. Available at www.yescarta.com. Accessed March 10, 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 3.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed March 10, 2021.
4. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed November 2, 2020.
5. National Comprehensive Cancer Network. Central Nervous System Cancers Version 3.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 2, 2020.

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 March 10, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	10.31.17	11.17
4Q 2018 annual review: added minimum ALC requirement per clinical trial exclusion criteria; clarified requirement of one anthracycline-containing regimen among the two lines of systemic therapy; added hematologist prescriber option; references reviewed and updated.	07.30.18	11.18
Added requirement in Section IA to confirm "Member does not have active or primary central nervous system (CNS) disease" to align with clinical trial exclusion criteria and NCCN recommendations; added to Section III "Active or primary CNS disease"; Appendix D was updated to include information related to CNS disease; removed requirement for CD19 tumor expression; references reviewed and updated.	07.16.19	08.19
4Q 2019 annual review: no significant changes; references reviewed and updated.	08.01.19	11.19
1Q 2020 annual review: no significant changes; references reviewed and updated.	10.31.19	02.20
Clarified history of or current secondary CNS disease is an exclusion in addition to active and primary CNS disease.	02.17.20	05.20
1Q 2021 annual review: clarified acceptable types of LBCL diagnoses per FDA indication and NCCN compendium; deleted active, primary, or secondary examples of CNS disease in Section I and III; references reviewed and updated.	11.02.20	02.21
Clarified Actemra authorization may be considered if requested.	03.18.21	
RT2: FL criteria added for newly approved indication; added criteria to LBCL indication for exclusion of concurrent and previous administration of CAR T-cell immunotherapy.	04.13.21	05.21

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

be bound by the foregoing terms and conditions, in addition to the Site Use Agreement for Health Plans associated with Envolve Pharmacy Solutions.