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| **Clinical Policy Title:** | axicabtagene ciloleucel |
| **Policy Number:** | RxA.323 |
| **Drug(s) Applied:** | Yescarta® |
| **Original Policy Date:** | 02/07/2020 |
| **Last Review Date:** | 06/10/2021 |
| **Line of Business Policy Applies to:** | All lines of business |

## Background

Axicabtagene ciloleucel is a CD19-directed genetically modified autologous T cell immunotherapy 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.
- Adult patients with 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).

Limitation(s) of use: Axicabtagene ciloleucel is not indicated for the treatment of patients with primary central nervous system lymphoma.

## Dosing Information

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| axicabtagene ciloleucel (Yescarta®) | LBCL, FL | IV Target dose: $2 \times 10^6$ CAR-positive viable T cells per kg body weight | $2 \times 10^8$ CAR-positive viable T cells |

## Dosage Forms

- Axicabtagene ciloleucel is available as a cell suspension for infusion. It comprises a suspension of $2 \times 10^6$ CAR-positive viable T cells per kg of body weight, with a maximum of $2 \times 10^8$ CAR-positive viable T cells in approximately 68 mL.

## Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

## I. Initial Approval Criteria

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

1. Diagnosis of LBCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. Recent (within the last 30 days) absolute lymphocyte count (ALC) of 100/µL or greater;
5. Disease is refractory or member has relapsed after 2 or more lines of systemic therapy that includes rituximab and one anthracycline-containing regimen (e.g., doxorubicin);
   **Prior authorization may be required for rituximab*;
6. Member does not have active or primary central nervous system (CNS) disease;
7. Member has not previously been treated with a CAR-T Therapy or axicabtagene ciloleucel;
8. Dose does not exceed 2 x $10^8$ chimeric antigen receptor (CAR)-positive viable T cells.

**Approval duration**
**Commercial:** 3 months (1 dose only)
**Medicaid:** 3 months (1 dose only)

**B. Follicular Lymphoma** (must meet all)**:**

1. Diagnosis of follicular lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Member is 18 years of age or older;
4. Disease is refractory or member has relapsed after 2 or more lines of systemic therapy that includes rituximab and an alkylating agent-containing regimen (e.g., cyclophosphamide);
   **Prior authorization may be required for rituximab;*
5. Member does not have active or primary central nervous system (CNS) disease;
6. Member has not previously been treated with a CAR-T Therapy or axicabtagene ciloleucel;
7. Dose does not exceed 2 x $10^8$ chimeric antigen receptor (CAR)-positive viable T cells.

**Approval duration**
**Commercial:** 3 months (1 dose only)
**Medicaid:** 3 months (1 dose only)

## II. Continued Therapy Approval

**A. All indications in Section I**

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

**Approval duration:** Not applicable

## III. Appendices

**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
LBCL: Large B-cell lymphoma
IV: Intravenous use
FL: Follicular lymphoma

**APPENDIX B: Therapeutic Alternatives**

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| **First-Line Treatment Regimens** | | |
| RCHOP (rituximab (Rituxan®),cyclophosphamide, doxorubicin, vincristine, prednisone) | Varies | Varies |
| RCEPP (rituximab (Rituxan®), cyclophosphamide, etoposide, prednisone, procarbazine) | Varies | Varies |
| RCDOP (rituximab (Rituxan®), cyclophosphamide, liposomal doxorubicin, vincristine, prednisone) | Varies | Varies |
| DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab (Rituxan®) | Varies | Varies |
| RCEOP (rituximab (Rituxan®), cyclophosphamide, etoposide, vincristine, prednisone) | Varies | Varies |
| RGCVP (rituximab (Rituxan®), gemcitabine, cyclophosphamide, vincristine, prednisone) | Varies | Varies |
| **Second-Line Treatment Regimens** | | |
| Bendeka® (bendamustine) ± rituximab (Rituxan®) | Varies | Varies |
| CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituximab (Rituxan®) | Varies | Varies |
| CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab (Rituxan®) | Varies | Varies |
| DA-EPOCH ± Rituxan® (rituximab) | Varies | Varies |
| GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab (Rituxan®) | Varies | Varies |
| gemcitabine, dexamethasone, carboplatin ± rituximab (Rituxan®) | Varies | Varies |
| GemOx (gemcitabine, oxaliplatin) ± rituximab (Rituxan®) | Varies | Varies |
| gemcitabine, vinorelbine ± rituximab (Rituxan®) | Varies | Varies |
| Revlimid® (lenalidomide) ± rituximab (Rituxan®) | Varies | Varies |
| rituximab (Rituxan®) | Varies | Varies |
| **Second-Line Treatment Regimens** | | |
| DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab (Rituxan®) | Varies | Varies |
| ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab (Rituxan®) | Varies | Varies |
| ICE (ifosfamide, carboplatin, etoposide) ± rituximab (Rituxan®) | Varies | Varies |
| MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab (Rituxan®) | 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 less than 100/µL were excluded.
- CRS, including fatal or life-threatening reactions, occurred in patients receiving axicabtagene ciloleucel. Do not administer axicabtagene ciloleucel 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 axicabtagene ciloleucel, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with axicabtagene ciloleucel. Provide supportive care and/or corticosteroids, as needed.
- The ZUMA-1 trial inclusion criteria required 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.
- Axicabtagene ciloleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Yescarta® REMS.

**References**

1. Yescarta® Prescribing information. Santa Monica, CA: Kite Pharma, Inc.; March 2021. Available at https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=9b70606e-b99c-4272-a0f1-b5523cce0c59&type=display . Accessed April 29, 2021.
2. Data on File. Kite Pharma – Yescarta®: Primary Results of the Pivotal ZUMA-1 Phase 2 Study. MRC-00038. April 2021.
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 April 29, 2021.
4. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed April 29, 2021.
5. National Comprehensive Cancer Network. Central Nervous System Cancers Version 5.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf . Accessed April 29, 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. Accessed April 26, 2021.

| Review/Revision History | Review/Revised Date | P&T Approval Date |
|---|---|---|
| Policy established. | 01/2020 | 02/07/2020 |
| Policy was reviewed:<br>1) Policy title was updated.<br>2) Background was updated.<br>3) Continued Therapy Approval criteria II.A.1 was rephrased.<br>4) Appendices updated.<br>5) References were updated. | 06/23/2020 | 09/14/2020 |
| Policy was reviewed:<br>1. Policy title was updated.<br>2. Dosing information updated.<br>3. FL indication and criteria added.<br>4. Clinical policy - Verbiage added: ‘‘The provision of provider samples does not guarantee coverage under the provisions of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage” after “Provider must submit…”<br>5. Appendices updated.<br>6. References were updated. | 04/29/2021 | 06/10/2021 |