Clinical Policy: Axicabtagene Ciloleucel (Yescarta)

Reference Number: PA.CP.PHAR.362
Effective Date: 10/2017
Last Review Date: 01/2024

Revision Log

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
  - That is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy
  - 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
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

All requests reviewed under this policy **require medical director review.**

It is the policy of PA Health & Wellness 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–h);
   a. DLBCL;
   b. Transformed Follicular Lymphoma (TFL) to DLBCL;
   c. Transformed Nodal Marginal Zone lymphoma (MZL) to DLBCL;

d. 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;
e. Monomorphic post-transplant lymphoproliferative disorders (B-cell type);
f. HIV-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL;
g. Monomorphic post-transplant lymphoproliferative disorders (B-cell type);
h. If request is for third line or later therapy, any of the following (i-vi):
   i. Primary mediastinal Large B-cell lymphoma (PMBCL);
   ii. Gastric MALT lymphoma;
   iii. Splenic marginal zone lymphoma;
   iv. Nongastric MALT lymphoma;
   v. Nodal marginal zone lymphoma;
   vi. Histologic transformation of indolent lymphomas to DLBCL;
   vii. Nodal marginal zone lymphoma;

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Recent (within the last 30 days) absolute lymphocyte count (ALC) ≥ 100/µL;
4. 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);
   **Prior authorization may be required for rituximab*
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®, Carvykti™, Kymriah™, Tecartus®):
7. Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma®, Breyanzi®, Carvykti™, Kymriah™, Tecartus®));
8. 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., Abecma, Breyanzi, Carvykti™, Kymriah, Tecartus);

7. Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Carvykti™, 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 for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53 for Medicaid.

II. Continued Therapy

A. All Indications in Section I:

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

B. Other diagnoses/indications:

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.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 – PA.CP.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

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 for all relevant lines of business 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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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), 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 and Tecartus REMS Program

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.
- ZUMA-1 and ZUMA-7 both excluded patients from these trials with history or presence of non-malignant CNS disorder, such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement.
- 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. In ZUMA-7, patients were required to have no known history or suspicion of CNS involvement by lymphoma. 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.; November 2022. Available at www.yescarta.com. Accessed October 4, 2023.
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 6.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed October 12, 2023.
4. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed October 12, 2023.
5. National Comprehensive Cancer Network. Central Nervous System Cancers Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed October 12, 2023.
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 12, 2023.

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 October 12, 2023.

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
2Q 2019 annual review: removed requirement for CD19 tumor expression; added minimum ALC requirement per clinical trial exclusion criteria; added hematologist prescriber option; references reviewed and updated.	04/2019
1Q 2020 annual review: 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; references reviewed and updated.	01/2020
1Q 2021 annual review: clarified acceptable types of LBCL diagnoses per FDA indication and NCCN compendium; references reviewed and updated.	01/2021
Clarified Actemra authorization may be considered if requested; 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; Added disclaimer under Policy/Criteria "All requests reviewed under this policy require medical director review."	07/2021
1Q 2022 annual review: added CAR T-cell immunotherapies into criteria; references reviewed and updated.	01/2022
1Q 2023 annual review: criteria revised per FDA approval for relapsed/refractory LBCL in the second-line setting; clarified for Primary Mediastinal Large B Cell Lymphoma (PMBCL) request is for third line or later therapy as this population was excluded in the ZUMA-7 second line setting clinical trial; per NCCN Compendium added the following LBCL supported uses: AIDS-related B-cell lymphomas, gastric MALT	01/2023

Reviews, Revisions, and Approvals	Date
lymphoma, splenic marginal zone lymphoma, nongastric MALT lymphoma; for LBCL added NCCN supported use in primary effusion lymphoma and HHV8-positive DLBCL; references reviewed and updated.	
1Q 2024 annual review: added the following NCCN compendium supported uses for LBCL: monomorphic post-transplant lymphoproliferative disorders (B-cell type), extranodal marginal zone lymphoma of the stomach, extranodal marginal zone lymphoma of nongastric sites (noncutaneous), nodal marginal zone lymphoma; revised reference from AIDS to HIV consistent with NCCN; references reviewed and updated.	01/2024