

**Clinical Policy: Axicabtagene Ciloleucel (Yescarta)**

Reference Number: CP.PHAR.362

Effective Date: 12.01.17

Last Review Date: 05.22

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)[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.
  - 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 (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 health plans affiliated with Centene Corporation® 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–g);
  - 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. AIDS-related B-cell lymphomas;
- g. If request is for third line or later therapy, any of the following (i-iv):
  - i. Primary mediastinal Large B-cell lymphoma (PMBCL);
  - ii. Gastric MALT lymphoma;
  - iii. Splenic marginal zone lymphoma;
  - iv. Nongastric MALT lymphoma;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age  $\geq$  18 years;
4. Recent (within the last 30 days) absolute lymphocyte count (ALC)  $\geq$  100/ $\mu$ L;
5. Request is for one of the following (a or b):
  - a. Disease is refractory or member has relapsed after  $\geq$  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*
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<sup>®</sup>, Carvykti<sup>™</sup>, Breyanzi<sup>®</sup>, Kymriah<sup>™</sup>, Tecartus<sup>®</sup>);
8. Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Breyanzi, Kymriah, Tecartus);
9. Dose does not exceed  $2 \times 10^8$  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  $\geq$  18 years;
4. Disease is relapsed/refractory after  $\geq$  2 lines of systemic therapy that includes a combination of an anti-CD20 monoclonal antibody (e.g., rituximab or Gazyva<sup>®</sup>) 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, Carvykti, Breyanzi, Kymriah, Tecartus);
7. Yescarta is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Breyanzi, Kymriah, Tecartus);

8. Dose does not exceed a single administration of  $2 \times 10^8$  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 (must meet 1 or 2):**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
  - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.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 (must meet 1 or 2):**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
  - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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	FDA: Food and Drug Administration
CAR: chimeric antigen receptor	FL: follicular lymphoma
CNS: central nervous system	LBCL: large B-cell lymphoma
CRS: cytokine release syndrome	MZL: marginal zone lymphoma
DLBCL: diffuse large B-cell 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
<b>LBCL First-Line Treatment Regimens</b>		
RCHOP (Rituxan <sup>®</sup> (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (Rituxan <sup>®</sup> (rituximab), cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCDOP (Rituxan <sup>®</sup> (rituximab), cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	Varies	Varies
DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + Rituxan <sup>®</sup> (rituximab)	Varies	Varies
RCEOP (Rituxan <sup>®</sup> (rituximab), cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies
RGCVP (Rituxan <sup>®</sup> , gemcitabine, cyclophosphamide, vincristine, prednisone)	Varies	Varies
<b>LBCL Second-Line Treatment Regimens</b>		
Bendeka <sup>®</sup> (bendamustine) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
DA-EPOCH ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
GDP (gemcitabine, dexamethasone, cisplatin) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies

<b>Drug Name</b>	<b>Dosing Regimen</b>	<b>Dose Limit/ Maximum Dose</b>
gemcitabine, dexamethasone, carboplatin ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
GemOx (gemcitabine, oxaliplatin) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
gemcitabine, vinorelbine ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
lenalidomide ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
Rituxan <sup>®</sup> (rituximab)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
DHAX (dexamethasone, cytarabine, oxaliplatin) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± Rituxan <sup>®</sup> (rituximab)	Varies	Varies
<b>FL First-Line and Second-Line + Subsequent Treatment Regimens</b>		
bendamustine + (Gazyva <sup>®</sup> (obinutuzumab) or rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + (Gazyva <sup>®</sup> (obinutuzumab) or rituximab)	Varies	Varies
CHOP + Gazyva <sup>®</sup> (obinutuzumab) or rituximab	Varies	Varies
CVP (cyclophosphamide, vincristine, prednisone) + Gazyva <sup>®</sup> (obinutuzumab)		
CVP + Gazyva <sup>®</sup> (obinutuzumab) or rituximab	Varies	Varies
rituximab ± (lenalidomide, chlorambucil, or cyclophosphamide)	Varies	Varies
rituximab	Varies	Varies
Gazyva <sup>®</sup> (obinutuzumab)	Varies	Varies
Zevalin <sup>®</sup> (ibritumomab tiuxetan)	Varies	Varies

*Therapeutic alternatives are listed as Brand name<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) 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: $2 \times 10^6$ CAR-positive viable T cells per kg body weight	$2 \times 10^8$ 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 2022. Available at [www.yescarta.com](http://www.yescarta.com). Accessed April 4, 2022.
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 2.2022. Available at: [https://www.nccn.org/professionals/physician\\_gls/pdf/b-cell.pdf](https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf). Accessed April 4, 2022.
4. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at [http://www.nccn.org/professionals/drug\\_compendium](http://www.nccn.org/professionals/drug_compendium). Accessed April 4, 2022.
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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. Bannani NN, Maurer MJ, Nastoupil LJ, et al. Experience with Axicabtagene Ciloleucel (Axicel) 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	P&T Approval Date
Clarified requirement of one anthracycline-containing regimen among the two lines of systemic therapy; clarified that policy is for HIM medical benefit and not for pharmacy benefit	04.23.18	
1Q 2019 annual review: added minimum ALC requirement per clinical trial exclusion criteria; added hematologist prescriber option; references reviewed and updated.	09.25.18	02.19
Removed requirement for CD19 tumor expression.	02.19.19	05.19
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.	07.16.19	08.19
1Q 2020 annual review: no significant changes; replaced HIM-Medical Benefit with HIM line of business; references reviewed and updated.	10.31.19	02.20
Clarified history of or current CNS disease is an exclusion.	02.17.20	05.20
1Q 2021 annual review: clarified acceptable types of LBCL diagnoses per FDA indication and NCCN compendium; references to HIM.PHAR.21 revised to HIM.PA.154; 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; Added disclaimer under Policy/Criteria “All requests reviewed under this policy require medical director review.”	04.13.21	05.21
1Q 2022 annual review: added pre-emptive indication for relapsed/refractory LBCL in the second-line setting; references reviewed and updated.	10.19.21	02.22
RT4: 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 lymphoma, splenic marginal zone lymphoma, nongastric MALT lymphoma; references reviewed and updated.	04.04.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.22.22	



**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. The Health Plan 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. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. 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. The Health Plan 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.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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**Note: For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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