Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Axicabtagene ciloleucel (Yescarta®)	MP-RX-FP-116-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drug

Service Description

This document addresses the use of Axicabtagene ciloleucel (Yescarta®), a CD19-directed genetically modified autologous T cell immunotherapy approved by the Food and Drug Administration (FDA) for the treatment of certain patients with large B-cell lymphoma, and follicular lymphoma (FL).

Background Information

Yescarta is a CD19-directed genetically-modified autologous T-cell immunotherapy, also known as chimeric antigen receptor (CAR) T- cell therapy. CAR T-cells are made by first collecting T-cells from the patient. The cells are then sent to a laboratory where they are genetically engineered to produce chimeric antigen receptors. The modified T-cells, now known as CAR T-cells, have the ability to better recognize an antigen (the CD19 protein) on targeted tumor cells. After the CAR T-cells have multiplied in the laboratory, they are then infused back into the patient. The modified CAR T-cells help the body's immune system better target and treat the tumor cells.

Yescarta has a black box warning for cytokine release syndrome (CRS), and should not be administered in patients with active infection or inflammatory disorders due to risk of life-threatening reactions and death. Severe or life-threatening CRS should be treated with tocilizumab with or without corticosteroids. Yescarta also has black box warning for causing neurological toxicities, which could also be severe and life-threatening. Monitoring for neurological events after administration is recommended. Due to these black box warnings, Yescarta is only available through a Risk Evaluation and Mitigation Strategy (REMS) program.

Definitions and Measures

- Allogeneic cells: Harvested from a histocompatible donor. Autologous cells: Harvested from the individual's own cells.
- Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.
- Chemotherapy: The medical treatment of a disease, particularly cancer, with drugs or other chemicals. Chimerism: Cell populations derived from different individuals; may be mixed or complete.
- Complete Response (CR): The disappearance of all signs of cancer as a result of treatment; also called complete remission; does not indicate the cancer has been cured.
- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living

abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:

- 0 = Fully active, able to carry on all pre-disease performance without restriction
- 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
- 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
- 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
- 5 = Dead

- Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.
- Line of Therapy:
  - First-line therapy: The first or primary treatment for the diagnosis, which may include surgery, chemotherapy, radiation therapy or a combination of these therapies.
  - Second-line therapy: Treatment given when initial treatment (first-line therapy) is not effective or there is disease progression.
  - Third-line therapy: Treatment given when both initial (first-line therapy) and subsequent treatment (second-line therapy) are not effective or there is disease progression.
- Refractory Disease: Illness or disease that does not respond to treatment.
- Relapse or recurrence: After a period of improvement, during which time a disease (for example, cancer) could not be detected, the return of signs and symptoms of illness or disease. For cancer, it may come back to the same place as the original (primary) tumor or to another place in the body.

Approved Indications

Yescarta FDA indication include:

- Treatment of adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.
- Treatment of adult patients with relapsed or refractory large B-cell lymphoma 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.
- Treatment of 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).

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It is important to note that Yescarta is not indicated for the treatment of patients with primary central nervous system lymphoma.

Other Uses

None

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	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 [Yescarta]

CPT Code	Description
0537T	Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day [for Yescarta]
0538T	Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage) [for Yescarta]
0539T	Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration [for Yescarta]
0540T	Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous [for Yescarta]

ICD-10 Procedure	Description
XW033C7	Introduction of engineered autologous chimeric antigen receptor T-cell immunotherapy into peripheral vein, percutaneous approach, new technology group 3 [when specified as Yescarta]
XW043C7	Introduction of engineered autologous chimeric antigen receptor T-cell immunotherapy into central vein, percutaneous approach, new technology group 3 [when specified as Yescarta]

ICD-10 Diagnosis	Description
C91.00-C91.02	Acute lymphoblastic leukemia
C82.00-C82.99	Follicular lymphoma
C83.30-C83.39	Diffuse large B-cell lymphoma
C85.20-C85.29	Mediastinal (thymic) large B-cell lymphoma
Z51.12	Encounter for antineoplastic immunotherapy

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Axicabtagene ciloleucel (Yescarta®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

Requests for Yescarta (axicabtagene ciloleucel) for **large B-cell lymphoma** may be approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**

ii. Individual has a histologically confirmed diagnosis of one of the following:
   - A. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; **OR**
   - B. High-grade B-cell lymphoma; **OR**
   - C. Primary mediastinal large B-cell lymphoma; **OR**
   - D. DLBCL from follicular lymphoma; **OR**
   - E. Monomorphic Post-Transplant Lymphoproliferative (B-cell type) Disorders (PTLD) (NCCN 2A); **OR**
   - F. AIDS-related B cell Lymphomas (NCCN 2A); **OR**
   - G. Nodal Marginal Zone Lymphoma (NCCN 2A); **OR**
   - H. Gastric MALT Lymphoma (NCCN 2A); **OR**
   - I. Nongastric MALT Lymphoma (Noncutaneous) (NCCN 2A); **OR**
   - J. Histologic Transformation of Indolent Lymphomas to DLBCL (NCCN 2A): **OR**
   - K. Splenic Marginal Zone Lymphoma (NCCN 2A);

AND

iii. Individual has all of the following:
   - A. Relapsed or refractory disease after receiving two or more lines of systemic therapy (which may or may not include therapy supported by autologous stem cell transplant), including all of the following:
     1. An anthracycline-containing chemotherapy regimen; **AND**
     2. For CD20-positive disease, anti-CD20 monoclonal antibody, such as rituximab; **AND**
     3. For those with DLBCL from follicular lymphoma, must have chemorefractory disease after transformation to DLBCL;

   OR

   - B. Relapsed or refractory disease (≤12 months) after first-line rituximab and anthracycline-based chemotherapy (Label, NCT03391466)

AND

iv. Individual has adequate bone marrow reserve defined by all of the following:
   A. Absolute neutrophil count (ANC) ≥ 1000 cells/uL; **AND**
   B. Absolute lymphocyte count (ALC) > 100 cells/uL; **AND**
   C. Platelet count ≥ 75,000 cells/uL; **AND**

v. If individual has a history of an allogeneic stem cell transplant, there are no signs of active graft versus host disease (GVHD); **AND**

vi. Individual has not received prior treatment with CAR T cell therapy or other genetically modified T-cell therapy; **AND**

vii. Individual has a current ECOG performance status of 0-1; **AND**

viii. Individual is using as a one-time, single administration treatment

Requests for Yescarta (axicabtagene ciloleucel) for **follicular lymphoma** may be approved if the following criteria are met:

i. Individual is 18 years of age or older; **AND**

ii. Individual has a diagnosis of relapsed or refractory follicular lymphoma Grade 1, 2, or 3A; **AND**

iii. Disease progression after two or more lines of systemic therapy with combination chemoimmunotherapy, including the following:
   A. Anti-CD20 monoclonal antibody, such as rituximab, combined with an alkylating agent; **AND**

iv. If individual has a history of an allogeneic stem cell transplant, there are no signs of active graft versus host disease (GVHD); **AND**

v. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; **AND**

vi. Individual has not received prior treatment with CAR-T cell therapy or other genetically modified T-cell therapy; **AND**

vii. Individual is using as a one-time, single administration treatment.

B. Criteria For Continuation of Therapy

i. Further treatment with Yescarta will not be authorized since it is designated for a single-dose administration as per its indication.

C. Authorization Duration

i. Initial Approval Duration: 3 months (1 dose only, tocilizumab (Actemra) will be approved if requested)

ii. Reauthorization Approval Duration: Not applicable

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D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

Yescarta (axicabtagene ciloleucel) for **large B-cell lymphoma** may not be approved for the following (Label, NCT02348216):

i. Repeat administration; **OR**
ii. Diagnosis of primary central nervous system lymphoma; **OR**
iii. Cardiac ejection fraction (EF) less than 40%, or other clinically significant cardiac disease; **OR**
iv. Using in combination with other chemotherapy agents (not including the use of lymphodepleting chemotherapy as labeled prior to Yescarta infusion); **OR**
v. History or presence of CNS disorders such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or autoimmune disease with CNS involvement); **OR**
vi. If prescribed in combination with other CAR T-cell immunotherapy (e.g. Abecma, Breyanzi, Carvykti, Kymriah, Tecartus); **OR**
vii. Individual has active GVHD; **OR**
viii. Active or latent hepatitis B, active hepatitis C, or other active, uncontrolled infection; **OR**
ix. When the above criteria are not met, and for all other indications.

Yescarta (axicabtagene ciloleucel) for **follicular lymphoma** may not be approved for the following (Label, NCT03105336):

i. Repeat administration; **OR**
ii. Presence or history of primary central nervous system lymphoma; **OR**
iii. Individual has a diagnosis of follicular lymphoma, grade 3B; **OR**
iv. History or presence of CNS disorders such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or autoimmune disease with CNS involvement; **OR**
v. Diagnosis of transformed follicular lymphoma, transformed marginal zone lymphoma, small lymphocytic lymphoma, or other aggressive lymphomas; **OR**
vi. Using in combination with other chemotherapy agents (not including the use of lymphodepleting chemotherapy prior to infusion); **OR**
vii. If prescribed in combination with other CAR T-cell immunotherapy (e.g. Abecma, Breyanzi, Carvykti, Kymriah, Tecartus); **OR**
viii. Individual has active GVHD; **OR**
ix. When the above criteria are not met, and for all other indications.

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Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule
Axicabtagene ciloleucel (Yescarta®)	The target dose is 2 × 106 CAR-positive viable T cells per kg body weight, with a maximum of 2 × 108 CAR-positive viable T cells.

Additional Information

- Yescarta is designated for autologous administration via intravenous infusion solely within a certified healthcare setting.
- Each single infusion bag of Yescarta contains a suspension of chimeric antigen receptor (CAR)-positive T cells in approximately 68 mL. Dosing of Yescarta is based on the number of chimeric antigen receptor (CAR)-positive viable T cells.
- **Pretreatment**: Yescarta should be initiated 2 days after completing lymphodepleting chemotherapy regimen with cyclophosphamide 500 mg/m^2/day intravenously (IV) and fludarabine 30 mg/m^2/day IV for 3 days.
- **Premedication** should include acetaminophen (650 mg orally) and diphenhydramine (12.5 mg i.v. or orally) approximately 1 hour 60 minutes before infusion of Yescarta. Prophylactic use of corticosteroids may be considered after weighing the potential benefits and risks.
- **Post-medication**: Tocilizumab plays an important role in the treatment of patients receiving CAR T-cell therapy such as Yescarta. It manages and mitigates cytokine release syndrome (CRS), which can occur after CAR T-cell infusion. Tocilizumab should be available to the patient prior to infusion and during the recovery period.

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Reference Information

1. CAR T-Cell Therapy Shows Durable Responses in Indolent NHL. Oncologist. 2020;25 Suppl 1(Suppl 1):S6-S7. doi:10.1634/theoncologist.2020-0559. Available at; https://theoncologist.onlinelibrary.wiley.com/doi/10.1634/theoncologist.2020- 0559.
2. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2021. URL: http://www.clinicalpharmacology.com. Updated periodically.
3. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: October 13, 2021.
4. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
5. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2021; Updated periodically.
6. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma [published online ahead of print, 2021 Dec 11]. N Engl J Med. 2021;10.1056/NEJMoa2116133. doi:10.1056/NEJMoa2116133 Available at: https://www.nejm.org/doi/pdf/10.1056/NEJMoa2116133?articleTools=true. Accessed April 15, 2022.
7. NCCN Clinical Practice Guidelines in Oncology™. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on October 13, 2021.
    i. B-Cell Lymphomas. V5.2021. Revised September 22, 2021.
    ii. NCT02348216. ClinicalTrials.gov. U.S. National Library of Medicine, National Institutes of Health website. Available at https://clinicaltrials.gov/ct2/show/NCT02348216?term=zuma-1&rank=1.
    iii. NCT03105336. ClinicalTrials.gov. U.S. National Library of Medicine, National Institutes of Health website. Available at https://clinicaltrials.gov/ct2/show/NCT03105336?term=NCT03105336&draw=2&rank=1.
    iv. NCT03391466. ClinicalTrials.gov. U.S. National Library of Medicine, National Institutes of Health website. Available at https://clinicaltrials.gov/ct2/show/NCT03391466.

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

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Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Adopted From Elevance	N/A	12/22/2023
Select Review	Update statement for criteria for initial approval: Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met all approval criteria.	Click or tap to enter a date.	Click or tap to enter a date.

Revised: 11/30/2023