

Subject: Chimeric Antigen Receptor T-cell Therapy (CAR T-cell): Yescarta (axicabtagene ciloleucel)		Original Effective Date: 4/12/18
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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

The intent of the policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references, and current peer-reviewed scientific literature. Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available. The information outlined in the MCP includes but is not limited to a review of evidence-based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

RECOMMENDATION

This policy addresses Yescarta (axicabtagene ciloleucel; axi-cel), an autologous chimeric antigen receptor (CAR) T-cell therapy, for the treatment of relapsed or refractory large B-cell lymphoma and follicular lymphoma.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

DESCRIPTION OF PROCEDURE/SERVICE/PHARMACEUTICAL

Large B-cell lymphoma (LBCL), a form of non-Hodgkin lymphoma (NHL), is characterized by an overproliferation of B cells of the immune system. NHL is a diverse group of distinct malignancies that originate from B cells or T cells. B-cell lymphomas account for approximately 85% of NHL cases in the United States. Patients diagnosed with a B-cell malignancy have a range of prognoses and treatment options that vary based on the stage of disease and whether it is considered relapsed or refractory (R/R). Signs and symptoms of NHL, such as diffuse large B-cell lymphoma (DLBCL), include enlarged lymph nodes; rapidly enlarging masses; fever, sweating, and chills; weight loss; fatigue; swollen abdomen; lack of appetite; chest pressure or pain; and shortness of breath. **DLBCL** is an aggressive form of NHL that affects B cells, interfering with a patient's immune response and ability to fight infection and is the most common type of NHL. Treatment options may include chemotherapy; immunotherapy; targeted therapy; radiation therapy; stem cell transplants; and, in rare cases, surgery. The current standard of care for the first-line treatment of DLBCL is chemotherapy with rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone (R-CHOP) [cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone] plus the monoclonal antibody rituximab (Rituxan) [[Lymphoma Research Foundation](#); [NCI](#)]. The treatment strategy for a first relapse or primary refractory disease is guided by the eligibility of ASCT, which depends on multiple factors, including medical fitness, presence of comorbidities, performance status, and patient preference. CAR T-cell therapy targeting CD19 is a treatment option for patients who have poor-risk DLBCL with no other treatment options that seem viable.

Follicular lymphoma (FL) is a type of B-cell lymphoma (BCL) and referred to as follicular since cancer cells tend to clump together in circles, known as follicles, in the lymph nodes. FL is a slow-growing or indolent form of NHL that arises from B-lymphocytes. Most FL cells have a specific chromosomal abnormality (a translocation between parts of chromosomes 14 and 18) that causes the overexpression of the gene BCL-2, which can cause the cells to become resistant to therapy (LLS, 2021). Patients with FL may have no obvious symptoms of the disease at diagnosis. Common symptoms of FL include enlargement of the lymph nodes in the neck, underarms, abdomen, or groin, as well as fatigue, shortness of breath, night sweats, and weight loss. Indolent NHL is a disease that starts out slowly but becomes more aggressive over time with each subsequent relapse. Treatment for indolent NHL ranges from observation with careful monitoring to aggressive therapy. Determining a treatment approach is based on multiple factors including prognostic factors, stage of disease, age and other medical conditions. FL is usually not considered to be curable, but more of a chronic disease. Currently, there are limited options for the treatment of R/R indolent FL after two or more lines of therapy.

Yescarta (axicabtagene ciloleucel; axi-cel) a gene-based immunotherapy, a form of CAR T-lymphocyte (T-cell) therapy, that involves adoptive cell transfer. Axi-cel is an autologous CAR T-cell therapy that targets the CD19 protein on the surface of cancer cells referred to as a CD19-directed CAR T cell therapy. T cells are collected from the patient and genetically modified using viral vectors to express CD19 cell receptors that are highly specific for B-lymphocyte (B-cell) antigens. The modified T cells are then infused back into the patient's body to target the patient's own B-cell malignancy. Yescarta is the first CAR T-cell therapy to receive FDA approval for large B-cell lymphoma and is also the first CAR T-cell therapy approved for patients with indolent follicular lymphoma.

FOOD AND DRUG ADMINISTRATION (FDA)

FDA-approved indication does not alone dictate coverage. MCP may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.

Follicular Lymphoma, relapsed or refractory (R/R FL)

Treatment of relapsed or refractory follicular lymphoma in adults after ≥ 2 lines of systemic therapy

Large B-cell lymphoma, relapsed or refractory (R/R LBCL)

Treatment of R/R LBCL in adults after ≥ 2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal LBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Limitations of use: Not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma

Available as: A suspension for intravenous infusion. Each single infusion bag of Yescarta contains a suspension of CAR-positive T cells in approximately 68 mL.

Approved by the FDA: October 18, 2017 (R/R LBCL); March 5, 2021 (R/R FL)

Boxed Warning Cytokine Release Syndrome (CRS), Neurologic Toxicities

- CRS, including fatal or life-threatening reactions, occurred in patients receiving axicabtagene ciloleucel. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurological 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.

Risk Evaluation and Mitigation Strategy (REMS): Yescarta is available only through a restricted program under a REMS called the [Yescarta and Tecartus REMS Program](#).

CLASSIFICATION: Antineoplastic Agent, Anti-CD19; Antineoplastic Agent, CAR-T Immunotherapy; CAR-T Cell Immunotherapy; Cellular Immunotherapy, Autologous; Chimeric Antigen Receptor T-Cell Immunotherapy

CENTERS FOR MEDICARE & MEDICAID SERVICES (CMS)National Coverage Determination (NCD) Manual 110.24

(Rev. 10454, Issued: 11-13-20, Effective: 08-07-19, Implementation: 02-16-21)

On August 7th, 2019 CMS published an NCD regarding CAR-T therapy coverage in the Medicare program. According to this NCD, for services performed on or after August 7, 2019, CMS covers autologous (your own blood-forming stem cells are collected) treatment for cancer with T-cells expressing at least one chimeric antigen receptor (CAR) when administered at healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies (REMS) and used for a medically accepted indication as defined at Social Security Act section 1861(t)(2) -i.e., is used for either an FDA-approved indication (according to the FDA-approved label for that product), or for other uses when the product has been FDA-approved and the use is supported in one or more CMS-approved compendia. Reference Publication 100-03, National Coverage Determination (NCD) **Manual Section 110.24** for complete coverage criteria.

NOTE: On 11/2020, a Change Request (CR) was issued to inform of coverage effective for claims with dates of service on or after August 7, 2019 [Link: [TN 10454 \(Medicare Claims Processing\)](#)]

COVERAGE CRITERIA FOR INITIAL AUTHORIZATION

Yescarta (axicabtagene ciloleucel) may be authorized as a one-time, single administration intravenous infusion when ALL the following criteria are met:

1. Prescriber specialty

- ☐ Prescribed by, or in consultation with, an oncologist/hematologist at a certified treatment center

2. Diagnosis/Indication/Step/Conservative Therapy [ALL]

Documentation of ALL of the following criteria are required. May include chart notes from the member's medical records, relevant labs and/or tests, and other relevant clinical information.

- ☐ Member meets ONE of the following **[A OR B]**

A. Large B-cell lymphoma, relapsed or refractory (R/R LBCL)

- ☐ Histologically confirmed diagnosis of ONE (1) of the following LBCL:
 - Diffuse large B-cell lymphoma (DLBCL)
 - Primary mediastinal large B-cell lymphoma (PMBCL)
 - High grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 translocations (also referred to as: double-hit or triple-hit lymphomas)
 - DLBCL arising from FL (also referred to as: FL with histological transformation to DLBCL)
 - Transformed Follicular Lymphoma (TFL) to DLBCL

NOTE: Yescarta will not be authorized for a diagnosis of primary CNS lymphoma

- ☐ ***Relapsed or refractory disease** defined as ONE or more of the following: [ONE]
 - ☐ Unable to achieve a complete remission following second line of systemic chemotherapy
 - ☐ Disease is in second or greater relapse/recurrence
 - ☐ Relapsed after autologous hematopoietic stem cell transplantation (HSCT)
 - ☐ Relapsed transplant ineligible disease

**Relapsed (appearance of a new lesion or $\geq 50\%$ increase in size of previously involved sites after a complete response) or refractory ($\geq 50\%$ increase from nadir in the size of any abnormal lesion or appearance of a new lesion during or following initial treatment).*

- ☐ Member has received **TWO or more lines** of systemic chemotherapy (which may or may not include therapy supported by stem cell transplant) **[AT LEAST TWO]**
 - ☐ Anti-CD20 monoclonal antibody (e.g., rituximab), UNLESS the tumor is CD20 negative or the member has an FDA-labeled contraindication to anti-CD20 therapy.
 - ☐ An anthracycline-containing chemotherapy regimen
 - ♦ *ZUMA-1 trial included only patients that received prior anti-CD20 antibody therapy and an anthracycline-containing regimen.*
 - ☐ For Transformed Follicular Lymphoma: Prior chemotherapy for follicular lymphoma with chemotherapy refractory disease after transformation to DLBCL

B. Follicular Lymphoma (FL) [ALL]

- ☐ Histologically confirmed diagnosis of indolent follicular lymphoma
- ☐ Relapsed or refractory indolent follicular lymphoma (grades 1-3a)^{ZUMA-5}
- ☐ Disease progression after TWO or more prior lines of treatment that included an anti-CD20 monoclonal antibody plus an alkylating agent.

3. Age/Gender/Other restrictions [ALL]

- ☐ Age 18 years or older
- ☐ Women of child-bearing potential: [ALL]
 - ☐ Negative serum pregnancy test within the past 30 days
 - AND
 - ☐ Prescriber attestation that member has been counseled on the use of effective contraception during treatment

4. Other Condition Requirements [ALL]

Documentation of all previous therapies required.

- ☐ Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

NOTE: ECOG performance status of 2 or greater does not meet criterion.

- ☐ ALL of the following clinical findings. Documentation required: [ALL]

- ☐ Absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$; and
- ☐ Absolute lymphocyte count (ALC) $> 100/\mu\text{L}$; and
- ☐ Platelet count $\geq 75,000/\mu\text{L}$

- ☐ Member has adequate bone marrow, cardiac, pulmonary, and organ function and deterioration are not expected within four (4) weeks after Yescarta (axi-cel) intravenous infusion, as determined by the treating oncologist/hematologist

NOTE: Lab results must be submitted within 14 days of the authorization confirming that member has adequate organ and bone marrow function and meets criteria

- ☐ For members with a history of allogeneic stem cell transplant only: Clinical documentation that member has no signs of active graft versus host disease (GVHD) required.

5. Exclusions/*Contraindications

**There are no contraindications listed in the manufacturer's labeling.*

- ☐ Absence of the following conditions: [ALL]

- ☐ Active CNS lymphoma as determined by appropriate testing or imaging (e.g. MRI and/or CSF analysis)
- ☐ Active inflammatory disorders
- ☐ Active graft versus host disease (GVHD)
- ☐ Fungal, bacterial, viral or any active infection(s) that is **uncontrolled*, including *but not limited to* the following: TB, active hepatitis B (HBsAG positive) or hepatitis C (anti-HCV positive), HIV

**Uncontrolled or requires IV antimicrobials (antibiotics, antifungals, antiprotozoals, antivirals)*

- ☐ History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
 - ◆ *NCCN guidelines define CNS involvement (CNS leukemia CNS-3) as the following: WBC count of ≥ 5 leukocytes/mcL in the CSF with the presence of lymphoblasts*
- ☐ Prior treatment with axicabtagene ciloleucel or other gene therapy; OR is being considered for treatment with other gene therapy
- ☐ Vaccination with live virus vaccines within the past 6 weeks (prior to the start of lymphodepleting chemotherapy)

☐ Member will not receive ANY of the following: [ANY]

- A G-CSF agent within the first 3 weeks after Yescarta infusion or until CRS has resolved;
 - ◆ *Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after CAR T cell infusion or until CRS has resolved. Levels of G-CSF and GM-CSF have been found to be elevated in patients with severe neurotoxicity and may be related to its development*
- Live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during treatment and until immune recovery following treatment with Yescarta

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful but are not sufficient documentation unless ALL specific information required by this MCP are included. [ALL]

- ☐ Clinical notes from member's medical records including: all relevant history and physical exams, disease staging, all prior therapies and cancer treatment history, anticipated treatment course applicable, labs and/or tests supporting the diagnosis (lab results must be dated within 14 days of request)
- ☐ Current weight for review of prescribed dosage

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

REAUTHORIZATION /CONTINUATION OF THERAPY

The safety and efficacy of repeat treatment has not been studied and is currently not supported by any compendia nor indicated in the current FDA approved labeling. Requests for reauthorization or beyond one dose is considered not medically necessary and will not be authorized.

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

Consult the manufacturer's labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.

Large B-Cell Lymphoma and Follicular Lymphoma

1. Recommended Dosage

Dosage prescribed is within the FDA-approved labeling:

- ☐ One treatment course consists of lymphodepleting chemotherapy [cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of Yescarta
- ☐ Target dose is 2×10^6 CAR-positive viable T cells per kg body weight, with a maximum dosage of 2×10^8 CAR-positive viable T cells

2. Authorization Limit

- ☐ Initial Authorization: ONE (1) single dose of Yescarta per lifetime
- ☐ Concurrent Authorizations: Authorizations for Yescarta will also receive approval of Actemra (tocilizumab) for up to 6 months with quantity limits appropriate for member's weight-based dose
 - ◆ *If severe or life-threatening CRS is suspected, administer Actemra as either 12mg/kg IV over 1 hour for patients <30kg or 8mg/kg IV over 1 hour for patients ≥30kg*
- ☐ Continuation of Treatment Authorization: NOT recommended.
 - ◆ *Repeat treatment of Yescarta for any indication is considered investigational, as the safety and efficacy beyond one dose has not been studied and is also not indicated in the current FDA approval for Yescarta. The evidence is insufficient to determine the effects on net health outcomes.*

3. Route of Administration [ALL]

- ☐ Yescarta (axi-cel) is considered a provider-administered medication via IV use only and must be administered in an [authorized treatment center](#)
- ☐ The treating facility is certified and complies with the Yescarta REMS requirements, including: [ALL]
 - Availability of a minimum of two doses of tocilizumab for each patient, if needed for treatment of CRS post-treatment
 - Member will be monitored for signs and symptoms of CRS for at least 4 weeks after treatment and counseled to seek immediate medical attention if signs or symptoms of CRS or a neurological event
 - Member is within proximity (2 hours) of the certified healthcare facility for at least 4 weeks post-treatment
 - Assurance that healthcare providers who prescribe, dispense, or administer Yescarta are trained in the management of CRS and neurologic toxicities

COVERAGE EXCLUSIONS

All other uses of Yescarta that are not an FDA-approved indication or not included in the ‘Coverage Criteria’ section of this policy are considered experimental/investigational or not a covered benefit of this policy, including but not limited to the following, due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcomes. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ☐ Members who have had prior treatment with any form of CAR T-cell therapy
 - ◆ *Repeat administration of Yescarta experimental and investigational since the safety and efficacy beyond one dose has not been studied and is not indicated in the current FDA approval for Yescarta. The evidence is insufficient to determine the effects on net health outcomes.*
- ☐ Pregnancy: There are no available data with Yescarta use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with Yescarta to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if Yescarta has the potential to be transferred to the fetus. Therefore, Yescarta is not recommended for women who are pregnant.
- ☐ Pediatric patients: The safety and efficacy of Yescarta have been established in pediatric patients; therefore, Yescarta is excluded in the pediatric population.
- ☐ Geriatric patients: Clinical trials of Yescarta did not include sufficient numbers of patients aged 65 years and older to determine they respond differently or have different safety outcomes as compared to younger patients.

SUMMARY OF EVIDENCE

Large B-cell Lymphoma, Relapsed or Refractory

The FDA approved the use of Yescarta for the treatment of patients with relapsed or refractory aggressive B-cell NHL based on the results from the ZUMA-1 clinical trial (Neelapu et al., 2017).

ZUMA-1 is a single-arm, open-label, multi-center Phase 2 trial with large B-cell NHL (DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma) who had previously received two treatments. Eligible patients had refractory disease or relapsed after autologous stem-cell transplantation; an ECOG performance status of 0 or 1; and had previously received an anti-CD20 monoclonal antibody containing-regimen and an anthracycline-containing chemotherapy.

- 111 patients enrolled; 101 patients received axi-cel (N=101); median age: 58 years (range 23 to 76 years)
Yescarta was manufactured for 110 patients and administered to 101 patients [1 patient was excluded due to unsuccessful manufacturing; 7 patients were excluded due to adverse events and/or tumor progression and 2 patients due to non-measurable disease]
- 77 patients with DLBCL, 8 patients with PMBCL, 16 patients with TFL; 85% had stage III or IV disease
- **69% of patients had received at least 3 prior lines of therapy; 77% had refractory disease to a second or greater line of therapy, and 21% had relapsed within 1 year of autologous HSCT**

- Axi-cel was administered as a single intravenous infusion at a target dose of 2×10^6 CAR-positive viable T cells/kg (maximum permitted dose: 2×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 500 mg/m² intravenously and fludarabine 30 mg/m² intravenously, both given on the fifth, fourth, and third day before axi-cel. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted.
- The median turnaround time for production of axi-cel was 17 days. All patients were hospitalized for axi-cel infusion and for a minimum of 7 days afterward.

Results

- **Among the 101 patients receiving axi-cel, the objective response rate was 82%. Complete response was observed in 54%. At a median follow up of 27.1 months, 83% of patients had a response and 58% had a complete response.**
- **Median time to response was observed to be 1 month (range: 0.8–6 months)**
- **Median duration of response of 8.1 months**
- **Grade 3 or higher adverse events occurred in 95% of patients;** neutropenia (78%), anemia (43%), and thrombocytopenia (38%) were the most common.
- **CRS of any grade occurred in 95% of treated patients;** grade 1 or 2 CRS was reported in 80% of patients, and 13% of patients had grade ≥ 3 CRS. 3 patients died during treatment; 2 deaths were related to axi-cel.

Long-term safety and activity of axi-cel in refractory LBCL (ZUMA-1): a single-arm, multicenter, phase 1-2 trial (Locke FL et al. 2019)

- After a median follow-up of 27.1 months in 101 patients from the ZUMA-1 study, axi-cel resulted in an objective response rate of 83% and 58% had a complete response. Median duration of response was 11.1 months.
- Median overall survival was not reached (12.8 to not estimable), with an estimated 24-month survival of 50.5% and the median progression-free survival 5.9 months
- In patients with double-expressor and high-grade B-cell lymphoma (n=33), an objective response rate occurred in 91% including a complete response in 70%.
- Grade 3 or worse events occurred in 98% of patients. Grade 3 or worse CRS (11%) and neurological events (32%) were manageable and mostly reversible
- This 2-year follow-up data from ZUMA-1 suggest that axi-cel can induce durable responses and a median overall survival of greater than 2 years and has a manageable long-term safety profile in patients with relapsed or refractory LBCL.

Four-year follow-up data from the pivotal ZUMA-1 trial of Yescarta in adult patients with refractory LBCL was reported at the American Society of Hematology (ASH) Annual Meeting and Exposition (Abstract #1187):

- Of 111 patients enrolled in the ZUMA-1 Phase 2 cohorts, Yescarta was administered to 101 patients with refractory LBCL, and the median time from leukapheresis to complete response was less than two months.
- There have been no Yescarta-related secondary malignancies reported and the four-year overall survival rate was 44 percent.

Follicular Lymphoma, relapsed or refractory (R/R FL)

The accelerated FDA approval was supported by data from the primary analysis of the Phase 2 ZUMA-5 trial. **ZUMA-5** is a single-arm, multicenter, open-label Phase 2 study that aims to enroll up to 160 adult patients (≥ 18 years old) with relapsed or refractory indolent NHL of either FL or marginal zone lymphoma (MZL) subtypes, who received at least two prior lines of systemic therapy, including an anti-CD20 monoclonal antibody combined with an alkylating agent.

ZUMA-5 is evaluating 146 adult patients (124 FL; 22 MZL) treated with Yescarta following two or more prior lines of therapy, including the combination of an anti-CD20 monoclonal antibody and an alkylating agent. The objectives of the study are to evaluate the efficacy and safety of a single infusion of Yescarta in this patient population. The primary endpoint of the trial is objective response rate as assessed by an independent review committee. Secondary endpoints include complete response rate, duration of response, progression-free survival, overall survival, safety and CAR T cell and cytokines levels. **The study is ongoing.**

- The most recent efficacy results of the trial showed 91% of patients with R/R FL (n=81) responded to one infusion of axi-cel and approximately 74% of patients in a continued remission at 18 months. This included 60% of patients who achieved a complete remission, and 13 of the 25 patients who achieved a partial remission also met imaging criteria for a complete remission but had not been confirmed by a negative bone marrow biopsy after treatment.
- Median duration of response among all patients with FL had not been reached at median follow-up of 14.5 months.
- 21% of patients experienced grade 3 or worse neurologic side effects and 8% experienced CRS
- The median time to onset of CRS was 4 days (range, 1-15) and the median duration of events was 6 days (range, 1-27). 99% of patients, however, had resolved events.
- The most common ($\geq 10\%$) grade 3 or higher adverse reactions included febrile neutropenia, encephalopathy, and infections with pathogen unspecified.
- **Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).**
- Estimated Primary Completion Date: February 2022

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

NCCN developed guidelines for the treatment of B-cell lymphoma with the following recommendation:

- Axicabtagene ciloleucel is indicated for the treatment of adult patients with r/r LBCL after ≥ 2 lines of systematic therapy, including DLBCL (not otherwise specified), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Several level 2A recommendations (*based upon lower-level evidence and uniform NCCN consensus that the intervention is appropriate*) are provided for the specific use of axicabtagene ciloleucel within clinical decision-making charts. ([NCCN B-Cell Lymphomas Guidelines](#))

National Institute for Health and Care Excellence (NICE)

NICE published a technology appraisal guidance ‘Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies’ [TA559]

The NICE recommends axicabtagene ciloleucel therapy for use within the Cancer Drugs Fund as an option for treating R/R DLBCL or PMLBCL in adults after 2 or more systemic therapies, if conditions in the managed access agreement are followed ([NICE 2019](#)).

The Institute for Clinical and Economic Review (ICER)

ICER published a final Evidence Report (March 2018) entitled Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value. ICER’s analyses reviewed outcomes for tisagenlecleucel in B-ALL and NHL and axicabtagene ciloleucel in NHL compared to outcomes in patients who received other therapies with similar FDA indications. Evidence is insufficient to judge whether one CAR T therapy is superior to the other for NHL. In general, the findings suggest that the CAR T therapies provide a net health benefit compared to standard chemoimmunotherapy regimens and found both therapies to be cost-effective in the long-term for the specified indications. However, at the current time there is uncertainty given that the studies of CAR T therapies are all single-arm trials that are small and have short follow-up. These uncertainties make the comparative efficacy analyses versus standard therapy controversial.

Hayes

A Precision Therapy Assessment addressing Axicabtagene Ciloleucel (Yescarta) for Treatment of Relapsed or Refractory B-Cell Malignancies was published Dec 11, 2020.

The report acknowledges that axi-cel is a treatment option for a patient population that generally has a poor prognosis and while axi-cel may have favorable survival outcomes based on available data, additional data are required to confirm these findings and provide a comparative context. The assessment concluded there is insufficient evidence to determine the relative efficacy and safety of axi-cel therapy among adult patients with R/R LBCL. The report notes there is substantial uncertainty regarding the safety and effectiveness of axi-cel therapy, due primarily to a lack of comparative studies and long-term follow-up data.

DEFINITIONS

Autologous transplantation: In autologous stem cell transplantation, the procedure uses the patient’s own stem cells for the transplant. The stem cells are collected from the patient in advance and are frozen. After the patient undergoes high doses of chemotherapy, either with or without radiation therapy, the stem cells are then returned to the body. This type of transplant is often used to treat blood cancers such as Hodgkin lymphoma, non-Hodgkin lymphoma and myeloma.

CAR-T cell therapy: Provides engineered molecules called chimeric antigen receptors (CARs) that recognize and destroy antigens present on the surface of lymphoma cells. T cells are removed from patients and genetically modified to produce CARs. The genetically engineered CAR-T cells are grown in the laboratory until they number in the billions and are then infused back into the patient.

CRS: An acute systemic inflammatory response syndrome characterized by fever, with or without multiple organ dysfunction that is associated with CAR-T cell therapy or other forms of immunotherapy. Clinical manifestations include fever, which may be accompanied by fatigue, headache, rash, diarrhea, arthralgia, and myalgia. Milder CRS can progress to a more severe syndrome, which may include hypotension, hypoxia, and uncontrolled systemic inflammatory response with circulatory collapse, vascular leakage, peripheral and/or pulmonary edema, renal failure, cardiac dysfunction, and multiorgan system failure.

Eastern Cooperative Oncology Group Performance Status (ECOG-PS)

A scale used to determine the individual's level of functioning; standard criteria for measuring how the disease impacts a patient's daily living abilities

- 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, e.g., light housework, 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 Deceased

The scale was developed by the ECOG, now part of the ECOG-ACRIN Cancer Research Group and published in 1982.

Refractory NHL is NHL that has not responded to initial treatment. Refractory disease may be disease that is getting worse or staying the same.

Relapsed NHL is NHL that responded to treatment but then returns.

APPENDIX

N/A

CODING INFORMATION

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is covered or non-covered. coverage is determined by the benefit document. This list of codes may not be all inclusive.

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]
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
0538T	Chimeric antigen receptor T-cell (CAR T) therapy; preparation of blood-derived T lymphocytes for transportation (e.g., cryopreservation, storage)
0539T	Chimeric antigen receptor T-cell (CAR T) therapy; receipt and preparation of CAR T cells for administration
0540T	Chimeric antigen receptor T-cell (CAR T) therapy; CAR T cell administration, autologous
ICD-10	Description
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
C91.00-C91.02	Acute lymphoblastic leukemia (ALL)

KEO June 3, 2021

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Policy History	Approval
<u>Policy Developed</u> IRO Peer Review: Policy was reviewed by practicing physician board certified in Internal Medicine, Oncology, Hematology, 11/21/2017	4/12/2018
<u>Policy Revision</u> IRO Peer Review: Policy was reviewed by practicing physician board certified in Oncology, 1/31/2019 <ul style="list-style-type: none"> • Previous policy (MCP-317) included both Kymriah and Yescarta; created individual policy for Kymriah (MCP-317a) and Yescarta (MCP-317b) • Notable revisions include: Revised coverage criteria in the Initial Recommendations; revisions in 'Exclusions' section; updated NCCN Clinical Practice Guidelines with summary from 'B-Cell Lymphomas Version 5.2018' 	3/11/2019
<u>Policy Revision</u> IRO Peer Review: Policy was reviewed by practicing physician board certified in Oncology, Hematology, 3/31/2020 Notable revisions include: <ul style="list-style-type: none"> • Added criterion for women of child-bearing potential requiring a negative pregnancy test • Added '<i>Long-term Safety and Efficacy Results of the ZUMA-1 trial</i>' in 'Summary of Medical Evidence' section • Added '<i>Lab results must be submitted within 14 days of the authorization</i>' to criterion confirming that member has adequate organ and bone marrow function • Updated criteria in the 'Recommendation' section: '<i>Member does NOT meet or have any of the following conditions</i>' to include '<i>Active CNS lymphoma by imaging</i>' and '<i>Vaccination with live virus vaccines within the past 6 weeks (prior to the start of lymphodepleting chemotherapy)</i>' • Updated NCCN Clinical Practice Guidelines with summary from 'B-Cell Lymphomas Version 2.2019' 	4/23/2020
<u>Annual Review</u> The medical necessity criteria were not revised with this annual review. Content updates and revisions include: <ul style="list-style-type: none"> • Updated NCCN guidelines on B-cell lymphoma (V.4.2020) recommendations for Yescarta • Insertion of a CMS Section outlining the NCD for implementation on 02-16-21 • Policy number updated to MCP-396 (from 317b) for clarity [Historical information: First policy developed was MCP-317 which included both Kymriah and Yescarta. Committee voted to split into individual policies for Kymriah (MCP-317a) and Yescarta (MCP-317b)] 	MCPC 2/8/21
<u>Revision</u> IRO Peer Review: Policy was reviewed by practicing physician board certified in Oncology, Hematology, 5/9/2021 Notable revisions include: <ul style="list-style-type: none"> • <u>Added the indication of Follicular Lymphoma (FL); FDA approved on March 5, 2021. Updated all content, clinical evidence, coverage criteria, practice guidelines, and reference sections related to FL.</u> • <u>Added the four-year follow-up data from the pivotal ZUMA-1 trial of Yescarta in adult patients with refractory LBCL.</u> 	MCPC 6/7/21

**Annual Review and Policy Revisions: All content, clinical evidence, coverage criteria, practice guidelines, appendices and reference sections were reviewed and revised with the most recent medical literature and available evidence. Coverage criteria for Initial and Continuation of Therapy were revised/updated as appropriate.*