**Yescarta (Axicabtagene Ciloleucel)**

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<th>Policy Number:</th>
<th>Original Effective Date:</th>
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<td>MM.02.037</td>
<td>07/01/2018</td>
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<tr>
<td>HMO; PPO; QUEST Integration</td>
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<th>Place(s) of Service:</th>
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<tbody>
<tr>
<td>Surgery</td>
<td>Inpatient</td>
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I. Description

Axicabtagene ciloleucel (Yescarta™) is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory large B-cell lymphoma 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. Axicabtagene ciloleucel is produced by engineering an individual’s own functioning immune cells to express tumor antigen recognition signals that target and destroy malignant cells in some types of cancer.

Background

**DIFFUSE LARGE B-CELL LYMPHOMA**

Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype of non-Hodgkin lymphoma and accounts for approximately 25% of non-Hodgkin lymphoma cases. DLBCL exhibits large heterogeneity in morphologic, genetic, and clinical aspects and multiple clinicopathologic entities are defined by the 2016 World Health Organization classification, which are sufficiently distinct to be considered separate diagnostic categories.

It has been estimated that 27,650 new cases of DLBCL were diagnosed in the United States in 2016. Treatment in the first-line setting (particularly rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is associated with a 5-year survival rate ranging from 60% to 70%. However, based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy. The response to subsequent salvage chemotherapy and consolidation with autologous cell transplantation is suboptimal. A 2017 retrospective analysis of the SCHOLAR-1 study, which pooled data from 2 phase 3 clinical trials and 2 observational cohorts, included 636 patients with refractory DLBCL. The objective response rate to the next line of therapy was 26%, with 7% achieving a complete response. Median overall survival was 6.3 months and 2-year survival was 20%. Refractory DLBCL was defined as progressive disease or stable disease as best response at any point during chemotherapy (>4 cycles of first-line or 2 cycles of later-line therapy) or as relapse 12 or fewer months after autologous cell transplantation.
**Axicabtagene Ciloleucel**

Similar to tisagenlecleucel, axicabtagene ciloleucel is an adoptive immunotherapy in which the T cells of a patient are modified genetically using a retroviral vector. The resulting genetically modified cells express a CD-19 directed chimeric antigen receptor protein that has a murine single-chain variable fragment with specificity for CD19. Once injected, the genetically modified T cells selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells.

**II. Criteria/Guidelines**

Axicabtagene Ciloleucel (Yescarta) is covered (subject to Limitations/Exclusions and Administrative Guidelines) when all of the following criteria are met:

A. The patient has been diagnosed with relapsed/refractory B-cell lymphoma* including any of the following:
   1. Diffuse large B-cell lymphoma (DLBCL) not otherwise specified; or
   2. Primary mediastinal large B-cell lymphoma; or
   3. High grade B-cell lymphoma; or
   4. Diffuse large B-cell lymphoma (DLBCL) arising from follicular lymphoma; and

B. The patient is 18 years of age or older; and

C. The patient has not previously been treated with gene therapy or Yescarta and/or being considered for treatment with any other gene therapy, and

D. The patient received adequate prior therapy which included all of the following:
   – anti-CD20 monoclonal antibody for CD20—positive tumor
   – anthracycline-containing chemotherapy regimen
   – for patients with transformed follicular lymphoma, prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease after transformation to diffuse large B-cell lymphoma

E. Documentation of all of the following:
   – absolute neutrophil count of >/ (greater or equal to) 1,000/uL
   – absolute lymphocyte count of > 100/uL
   – platelet count of >/ (greater or equal to) 75,000 /uL

F. The patient will not be treated with more than $2.0 \times 10^8$ CAR-positive viable T cells; AND

G. If the patient is under 100kg in weight, they will receive weight-based dosing $2.0 \times 10^6$ CAR-positive viable T cells; and

H. The patient has received or will receive lymphodepleting cyclophosphamide 500mg/m² intravenously and fludarabine 30 mg/m² intravenously on the fifth, fourth, and third day before infusion of Yescarta; and

I. The patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; and

J. The patient does not have primary central nervous system (CNS) lymphoma; and

K. The patient does not have human immunodeficiency virus (HIV), active Hepatitis B or C, active uncontrolled infection and any autoimmune disease requiring immune suppression; and
L. The prescriber will submit documentation of response to Yescarta within 3 months following therapy as a follow-up to the prior approval request.
* Relapsed or refractory disease, defined as progression after 2 or more lines of systemic therapy.

III. Limitations/Exclusions

A. Axicabtagene ciloleucel is considered investigational and not medically necessary as a treatment for relapsed or refractory non-Hodgkin’s lymphoma when the medically necessary criteria are not met, and for all other indications, including but not limited to:
   1. Any central nervous system (CNS) disease (for example, brain metastases, CNS lymphoma, and a history or presence of CNS disorders such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or autoimmune disease with CNS involvement);
   2. History of allogeneic stem cell transplant, chimeric antigen receptor therapy or other genetically modified T-cell therapy;
   3. Active, uncontrolled infection;
   4. Human immunodeficiency virus (HIV);
   5. Hepatitis B or C (if viral load is detectable).

B. Other applications of Axicabtagene ciloleucel are not covered.

IV. Administrative Guidelines

A. Precertification is required. To pre-certify, complete HMSA’s Precertification Request form and fax or mail the form, or use iExchange with the following documentation:
   1. Clinical notes of past and current treatment
   2. Confirmation of diagnosis (e.g. imaging, path)
   3. Recent labs

B. Applicable codes:

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<th>CPT Codes</th>
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<tr>
<td>J9999</td>
<td>Not Otherwise Classified, Antineoplastic Drugs</td>
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<td>J3490</td>
<td>Unclassified Drugs</td>
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<tr>
<td>J3590</td>
<td>Unclassified Biologics</td>
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<tr>
<td>0537T</td>
<td>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</td>
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<tr>
<td>0538T</td>
<td>Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage)</td>
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<td>HCPCS Codes</td>
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<tr>
<td>Q2041</td>
<td>Axicabtagene Ciloleucel, up to 200 Million Autologous Anti-CD19 CAR T Cells, Including Leukapheresis And Dose Preparation Procedures, Per Infusion</td>
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<td>XW033C3; XW043C3</td>
<td>New technology codes for Engineered Autologous Chimeric Antigen Receptor T-cell Immunotherapy, peripheral vein and central vein codes</td>
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V. Scientific Background

**Axicabtagene Ciloleucel**

For individuals who are adults with histologically confirmed diagnosis of aggressive non-Hodgkin lymphoma (eg, diffuse large B-cell lymphoma not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, transformed follicular lymphoma) who receive axicabtagene ciloleucel, the evidence includes a single-arm prospective trial. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related mortality and morbidity. The pivotal single-arm trial reported a 72% overall response rate (measured by complete or partial remission) in heavily pretreated patients. After a median follow-up of 7.9 months, the median duration of response was 9.2 months. The observed benefits were offset by a high frequency and severity of adverse reactions. Cytokine release syndrome was observed in more than half (94%) of the patients, and 13% had an adverse event at grade 3 or higher. Long-term follow-up and real-world evidence is required to assess the generalizability of axicabtagene ciloleucel efficacy and safety outside of the clinical trial setting. The manufacturer has agreed to a postmarketing requirement observational registry study to collect safety information for patients treated with the marketed product. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

On October 18, 2017, the U.S. Food and Drug Administration (FDA) approved axicabtagene ciloleucel for the treatment of adults 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”. Axicabtagene ciloleucel was granted breakthrough and priority review status by the FDA (Product Information [PI] Label, 2017).
FDA approval was based on the results of a single arm, open-label, multicenter, phase 1/2 study (ZUMA-1) in 111 adults (18 years and older) diagnosed with DLBCL, primary mediastinal B-cell lymphoma or transformed follicular lymphoma, which are types of aggressive NHL (Neelapu, 2016). A total of 101 study participants were successfully treated with a single infusion of axicabtagene ciloleucel. All study enrollees received lymphodepleting chemotherapy (fludarabine and cyclophosphamide) prior to infusion with the axicabtagene ciloleucel. Inclusion criteria included chemotherapy refractive disease, prior treatment with an adequate chemotherapy regimen, at least one measurable lesion per revised International Working Group (IWG) Response Criteria, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, absolute neutrophil count (ANC) ≥ 1000/uL, absolute lymphocyte count (ALC) > 100/uL, platelet count ≥ 75,000/uL, and adequate organ function. Study exclusion criteria included a history of malignancy other than non-melanoma skin cancer or carcinoma in situ (for example, cervix, bladder, breast), history of allogeneic stem cell transplantation, prior therapy with a genetically modified T-cell therapy, presence of an uncontrolled infection, positive for human immunodeficiency virus (HIV), hepatitis B or C virus (history of hepatitis B or C is permitted if the viral load is undetectable per quantitative polymer chain reaction [PCR] and/or nucleic acid testing), subjects with detectable central nervous system (CNS) disease, or brain metastases, a history of CNS lymphoma, or a history or presence of CNS disorders such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement. The study met its primary endpoint with an objective response rate of 72% (p<0.0001); 51% complete responses and 21% partial responses. With a median follow-up of 8.7 months, the median overall survival has not yet been reached. The overall duration of response was 9.2 months and has not yet been reached in those who achieved a complete response. The most common grade 3 or higher adverse events included decreased lymphocyte count (100%), decreased white blood cell count (96%), neutropenia (93%), anemia (66%), thrombocytopenia (58%) and encephalopathy (29%). Other grade 3 or higher serious adverse events that occurred in study participants included hemophagocytic lymphohistiocytosis (1%), cardiac failure (6%), cardiac arrest (4%), cytokine release syndrome (13%), and pulmonary edema (9%) (PI Label, 2017).

The National Comprehensive Cancer Network® (NCCN®) Clinical Practice Guidelines (CPG) for NHL (2017) does not currently have a recommendation for the use axicabtagene ciloleucel as a therapeutic option in the treatment of NHL.

Axicabtagene ciloleucel is also being investigated for safety and efficacy in combination with atezolizumab for NHL, in children and young adults with NHL, and for the treatment of adults with relapsed/refractory acute lymphoblastic leukemia (ALL), multiple myeloma and mantle cell lymphoma (ClinicalTrials.gov, 2017).

VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.
Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References
