Chimeric Antigen Receptor T cell Therapy (CAR-T)

Policy # 00605
Original Effective Date: 02/21/2018
Current Effective Date: 02/21/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Other forms of adoptive immunotherapy such as using adoptive cellular therapy for the administration of cytotoxic T lymphocytes, cytokine-induced killer cells, tumor-infiltrating lymphocytes, or antigen-loaded autologous dendritic cells are addressed separately in medical policy 00248.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

**tisagenlecleucel (Kymriah™)**

Based on review of available data, the Company may consider the use of tisagenlecleucel (Kymriah) for the treatment of relapsed or refractory B cell acute lymphoblastic leukemia (ALL) to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for the use of tisagenlecleucel (Kymriah) will be considered when ALL of the following criteria are met:

- Patient has a confirmed diagnosis of CD19-positive B-cell ALL with morphologic bone marrow tumor involvement (>5% lymphoblasts); AND
- Patient is 25 years old or younger at time of infusion; AND
- Disease is refractory to initial therapy or in second or later relapse
  - Refractory is defined as failure to obtain complete response with induction therapy, i.e., failure to eradicate all detectable leukemia cells (<5% blasts) from the bone marrow and blood with subsequent restoration of normal hematopoiesis (>25% marrow cellularity and normal peripheral blood counts);
  - Relapsed is defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission (CR) with chemotherapy and/or allogeneic stem cell transplant; AND
- Patient has NOT received prior treatment with Kymriah or any other gene therapy and is not being considered for treatment with any other gene therapy; AND
  (Note: This specific criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).
- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  (Note: This specific criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met).
- Patient does NOT have any of the following:

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**axicabtagene ciloleucel (Yescarta™)**

Based on review of available data, the Company may consider the use of axicabtagene ciloleucel (Yescarta) for the treatment of relapsed or refractory B-cell lymphoma to be **eligible for coverage.**

**Patient Selection Criteria**

Coverage eligibility for the use of axicabtagene ciloleucel (Yescarta) will be considered when ALL of the following criteria are met:

- Patient has a documented diagnosis of one of the following:
  - Diffuse large B-cell lymphoma (DLBCL), not otherwise specified; OR
  - Primary mediastinal large B-cell lymphoma; OR
  - High grade B-cell lymphoma; OR
  - DLBCL arising from follicular lymphoma; AND
- Patient is > 18 years old at the time of infusion; AND
- Disease is relapsed or refractory, defined as progression after 2 or more lines of systemic therapy (which may or may not include therapy supported by autologous cell transplant); AND
- Patient has failed two or more lines of systemic therapy including:
  - Anti-CD20 monoclonal antibody (such as rituximab) unless tumor is CD20-negative; AND
  - An anthracycline containing chemotherapy regimen; AND
  - Patient has NOT received prior treatment with Yescarta or any other genetically modified T cell therapy and is not being considered for treatment with any other gene therapy; AND

*(Note: The criteria requiring specific systemic agents are additional company requirements for coverage eligibility and will be denied as not medically necessary** if not met. If patient has not failed two or more lines of any systemic therapy, request will be denied as investigational)*

*(Note: This criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
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- Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis; AND
  (Note: This criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)
- Patient has documentation of ALL of the following at the time of infusion:
  - Absolute neutrophil count ≥1000/µL; AND
  - Absolute lymphocyte count >100/µL; AND
  - Platelet count ≥75,000/µL; AND
  (Note: These criteria are additional company requirements for coverage eligibility and will be denied as not medically necessary** if not met)
- Patient does NOT have ANY of the following:
  - Primary CNS lymphoma; OR
  - Active CNS disease (e.g. seizure disorder, CV ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement); OR
  (Note: This criterion is an additional company requirement for coverage eligibility and will be denied as not medically necessary** if not met)
  - Active hepatitis B, hepatitis C, human immunodeficiency virus (HIV), or other uncontrolled fungal, bacterial, or other viral infection requiring intravenous antimicrobials

When Services Are Considered Not Medically Necessary
Based on review of available data, the Company considers the use of tisagenlecleucel (Kymriah) or axicabtagene ciloleucel (Yescarta) when the patient has received prior treatment with chimeric antigen receptor T cell therapy (CAR-T) or other gene therapy, when the patient does not have adequate organ function, or has active CNS disease to be not medically necessary.**

Based on review of available data, the Company considers the use of tisagenlecleucel (Kymriah) when the patient has Burkitt lymphoma, has a concomitant genetic syndrome (other than Down syndrome), has grade 2-4 graft-vs-host disease, or has received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion to be not medically necessary.**

Based on review of available data, the Company considers the use of axicabtagene ciloleucel (Yescarta) when the patient has not failed at least one anti-CD20 monoclonal antibody (unless tumor is CD20 negative), has not failed an anthracycline containing chemotherapy regimen, or does not meet pre-specified blood counts at the time of infusion to be not medically necessary.**

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.
Based on review of available data, the Company considers the use of tisagenlecleucel (Kymriah) or axicabtagene ciloleucel (Yescarta) when patient selection criteria are not met (except those listed as not medically necessary**) to be investigational.*

**Background/Overview**

CAR-T is a form of adoptive immunotherapy in which a patient's own T cells are removed and programmed to destroy cells marked with a certain protein. In the case of Kymriah and Yescarta, that protein is CD-19 which is expressed on most B cells. These drugs are therefore indicated for certain cancers involving proliferation of B cells.

Kymriah is a CAR-T therapy currently approved for the treatment of relapsed or refractory ALL in patients younger than 25 years of age. Treatment involves reprogramming a patient’s own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing cells. The patient’s T cells are removed and reprogrammed in vitro then re-infused at a rate of 10-20 mL/min. The recommended dosage of Kymriah for patients 50 kg or less is 0.2 to 5.0×10^6 chimeric antigen receptor (CAR)- positive viable T cells per kilogram of body weight intravenously; for patients above 50 kg, dose is 0.1 to 2.5×10^8 total CAR-positive viable T cells (non-weight-based) intravenously. Prior to infusion, the patient must be pre-treated with fludarabine and cyclophosphamide to deplete the patient’s lymphocytes and reduce the risk of severe cytokine release syndrome (CRS). CRS is one of the most common adverse effects occurring in 79% of patients in the pivotal trial. Severe CRS may be life-threatening and should be treated with tocilizumab. Due to the potential for severe CRS, the drug is only available through a Risk Evaluation and Mitigation Strategy (REMS) program to ensure that providers are aware of the signs of CRS and able to appropriately treat severe CRS.

Yescarta is a CAR-T therapy currently approved for the treatment of adults with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy. Similar to Kymriah, Yescarta is an adoptive immunotherapy in which the T cells of a patient are modified genetically to selectively target and bind to CD19 antigen expressed on the surface of normal and malignant B cells. Prior to infusion of Yescarta, the patient must be pre-treated with a lymphodepleting chemotherapy regimen of cyclophosphamide and fludarabine. The recommended dosage of Yescarta is 2 x 10^6 CAR-positive viable T cells per kilogram body weight with a maximum of 2 x 10^8 CAR-positive viable T cells. After infusion of Yescarta, patients must be monitored at least daily for 7 days at a certified healthcare facility for signs and symptoms of CRS and neurologic toxicities and then remain within proximity of the certified healthcare facility for at least 4 weeks following infusion. As with Kymriah, CRS occurs frequently in Yescarta-treated patients resulting in the drug being restricted through a REMS program. Both the Kymriah and the Yescarta REMS programs require health care facilities that dispense and administer the drugs to comply with the following requirements:

- Certified facilities must have onsite, immediate access to tocilizumab, and ensure that a minimum of 2 doses of tocilizumab are available for each patient for administration within 2 hours after Kymriah or Yescarta infusion, if needed for treatment of CRS.
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- Certified facilities must ensure that health care providers who prescribe, dispense, or administer Kymriah or Yescarta are trained to manage CRS and neurologic toxicities.

**Acute lymphoblastic leukemia (ALL)**

ALL is one of the most common childhood malignancies. Despite having a relatively high 5 year overall survival rate of 85%, prognosis is poor for those who do not respond to initial treatment. Relapse following ALL treatment is the second most common cause of cancer-related death in children. Initial treatment is approached in three stages: induction, consolidation, and maintenance. The goal of induction therapy, which usually lasts 3-4 weeks, is to achieve an initial CR. If CR is not reached during this stage, the disease is considered refractory. Consolidation treatment is designed to prevent leukemic regrowth, reduce residual tumor burden, and prevent emergence of drug resistance in the remaining leukemic cells. This phase typically lasts 4-8 months and includes drugs tailored to the patient based on risk of re-occurrence. The final phase of treatment, the maintenance phase, is a less intensive continuation regimen of daily therapy that is continued for a total treatment duration of 30-42 months. Re-occurrence after completion of the maintenance phase is considered relapse and requires aggressive reinduction therapy and intensification, which is often ineffective. Patients who achieve a second remission are candidates for allogeneic hematopoietic stem cell transplantation. Relapse of ALL can occur in many extramedullary sites, but most often occurs in the bone marrow, CNS, or testicles. Bone marrow relapse is the most common site of relapse and usually presents with persistent peripheral blood cytopenias. When the relapse occurs in the CNS, the NCCN guidelines classify the disease into the following categories:

- CNS 1: No lymphoblasts in cerebrospinal fluid (CSF) regardless of the white blood cell (WBC) count;
- CNS 2: WBC<5/µL in CSF with presence of lymphoblasts;
- CNS 3: WBC >5/µL in CSF with presence of lymphoblasts.

**Diffuse large B-cell lymphoma (DLBCL)**

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 60-70%. However, based on a number of prognostic factors, 20-50% 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 with one study finding only 7% of patients with refractory DLBCL achieving a complete response to the next line of therapy.
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FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
Kymriah is FDA approved for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.

Yescarta is FDA approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. FDA approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Kymriah was approved based on an open-label, multicenter single-arm trial including 63 patients treated with lymphodepleting chemotherapy followed by a single dose of Kymriah. Efficacy endpoints included achievement of CR within 3 months after infusion, duration of CR, and proportion of patients with CR and minimal residual disease (MRD)<0.01% by flow cytometry. CR designation required remission status to be maintained for at least 28 days without clinical evidence of relapse. 83% of patients achieved a CR or CR with incomplete blood count recovery (CRi), and all patients were negative for MRD. Median duration of remission was not reached at the time that the study data was submitted (median follow-up of 4.8 months from response).

Patients were only included in the study if they had adequate organ function defined based on measures of serum creatinine, alanine aminotransferase, bilirubin, pulse oxygenation, and left ventricular ejection fraction. In addition, Kymriah was not studied in patients with extra-medullary disease relapse, Burkitt lymphoma, or concomitant genetic syndromes that pre-dispose patients to leukemia, such as Fanconi anemia or Kostmann syndrome. Patients with Down syndrome were not excluded.

It is important to note that adequate organ function was defined as follows:

- Serum Creatinine within normal limits for patient age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Serum Creatinine (mg/dL)</th>
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<tbody>
<tr>
<td>1-&lt;2</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>2 - &lt;6</td>
<td>&lt;0.8</td>
</tr>
<tr>
<td>6-&lt;10</td>
<td>&lt;1</td>
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<td>10-&lt;13</td>
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<table>
<thead>
<tr>
<th>Age Group</th>
<th>ALT Limit</th>
<th>Bilirubin Limit</th>
<th>Pulmonary Reserve</th>
<th>LVSF Limit</th>
</tr>
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<tbody>
<tr>
<td>&lt;16</td>
<td>&lt;1.5 (Male) &lt;1.4 (Female)</td>
<td>&lt;2.0 mg/dL</td>
<td>&gt; Grade 1 dyspnea and pulse oxygenation &gt;91% on room air</td>
<td>&gt;28% confirmed by echocardiogram or Left Ventricular Ejection Fraction &gt;45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition</td>
</tr>
<tr>
<td>&gt;16</td>
<td>&lt;1.7 (Male) &lt;1.4 (Female)</td>
<td>&lt;2.0 mg/dL</td>
<td>&gt; Grade 1 dyspnea and pulse oxygenation &gt;91% on room air</td>
<td>&gt;28% confirmed by echocardiogram or Left Ventricular Ejection Fraction &gt;45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition</td>
</tr>
</tbody>
</table>

- Alanine aminotransferase (ALT) <5 times the upper limit of normal (ULN) for age
- Bilirubin <2.0 mg/dL
- Minimum level of pulmonary reserve < Grade 1 dyspnea and pulse oxygenation >91% on room air
- Left Ventricular Shortening Fraction >28% confirmed by echocardiogram or Left Ventricular Ejection Fraction >45% confirmed by echocardiogram or Multiple Uptake Gated Acquisition

Yescarta was approved based on the results of an open-label, multicenter phase 1/2 study, which reported CR rates and duration of response demonstrated in the phase 2 portion of the study. Adults with aggressive B-cell non-Hodgkin lymphoma that was primary refractory, refractory to a second or greater line of therapy, or relapsed within 1 year after autologous hematopoietic cell transplantation were enrolled in the study. Patients with prior allogeneic hematopoietic cell transplantation, any history of CNS lymphoma, Eastern Cooperative Oncology Group Performance Status score of 2 or greater, absolute lymphocyte count less than 100/µL, creatinine clearance less than 60 mL/min, hepatic transaminases more than 2.5 times the ULN, cardiac ejection fraction less than 50%, or active serious infection were excluded. Most patients (74%) had de novo DLBCL and 32% had double- or triple-hit lymphoma. The median age was 58, with 24% being aged 65 years or older; the median number of prior therapies was 3; 77% had refractory disease to a second or greater line of therapy; and 21% had relapsed within 1 year after autologous hematopoietic cell transplantation (HCT).

All patients received a lymphodepleting regimen consisting of cyclophosphamide and fludarabine prior to infusion of Yescarta. Of the 111 patients who underwent leukapheresis, 101 received the infusion (9 were not treated due to progressive disease or serious adverse reactions following leukapheresis and there was a manufacturing failure in 1 patient). Study protocol mandated hospitalization of patients for infusion and 7 days after infusion. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. The median time from leukapheresis to product delivery was 17 days. The primary end point was objective response rate based on a modified intention-to-treat population, which was defined as all patients treated with at least 1.0 x 10^6 CAR-T cells per kilogram. Objective response was seen in 72% of patients with 51% achieving a complete response and 21% achieving a partial response.

References
2. Tisagenlecleucel (Kymriah) [Package Insert], Novartis, East Hanover, New Jersey Updated Aug 30, 2017.
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**Policy History**

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02/01/2018 Medical Policy Committee review
02/21/2018 Medical Policy Implementation Committee approval. New policy
04/01/2018 Coding update
05/22/2018 Coding update

Next Scheduled Review Date: 02/2019

**Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<td>J3490, J3590, J9999, Q2040</td>
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</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:
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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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