Medicare Advantage Medical Benefit Drug Policy

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Effective Date: 08/12/2021

Kymriah™ (tisagenlecleucel)

FDA approval: 05/1/20218
HCPCS: Q2042
Benefit: Medical

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Prescribed by or in consultation with an oncologist
   b. Diagnosis of pediatric and young adult with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory[a] or in second or later relapse[b]:
      i. FDA approved age
      ii. Primary refractory as defined by not achieving a complete response after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a complete response after 1 cycle of standard chemotherapy for relapsed leukemia
      iii. Patients with Philadelphia chromosome positive (Ph+) ALL are eligible if they are intolerant to or have failed 2 lines of tyrosine kinase inhibitor therapy (TKI), or if TKI therapy is contraindicated
      iv. Any bone marrow (BM) relapse after allogenic SCT
      v. Do not have any of the following:
         1. Burkitt's lymphoma
         2. Active hepatitis B, C
         3. Any uncontrolled infection
         4. Grade 2 to 4 graft-versus-host disease
         5. Concomitant genetic syndrome with the exception of Down's syndrome
         6. Received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to tisagenlecleucel infusion
      vi. Documentation of CD 19 tumor expression
   c. Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma:
      i. FDA approved age
      ii. Received ≥ 2 lines of chemotherapy, including rituximab and anthracycline
      OR
      iii. Relapsed following autologous hematopoietic stem cell transplantation (HSCT)

iv. Documentation of CD 19 tumor expression
v. Do not have any of the following:
    1. Active central nervous system malignancy as determined by appropriate testing. Examples include: MRI and/or CSF analysis (including cytology plus molecular analysis, for example FISH)
    2. Prior allogenic HSCT
    3. ECOG performance status ≥ 2
    4. Creatinine clearance < 60 mL/min
    5. Alanine aminotransferase > 5 times normal
    6. Cardiac ejection fraction < 45%
    7. Absolute lymphocyte concentration less than 300/µL

d. Have not received prior treatment with any CAR-T therapy despite indication or any other genetically-modified T-cell therapy or are being considered for treatment with any other genetically-modified T-cell therapy
e. Only to be administered at certified bone marrow/stem cell transplant centers
f. Trial and failure, intolerance, or a contraindication to the preferred products as listed in the BCBSNE Part B drugs prior authorization list
g. The prescriber needs to submit documentation of response to Kymriah within 3 months following therapy as a follow-up to the prior approval request.
h. If new diagnoses are FDA approved, coverage will be determined based on the FDA approved indication on a case by case basis until fully evaluated by the Pharmacy and Therapeutics Committee

B. Quantity Limitations, Authorization Period and Renewal Criteria
    a. Quantity Limits: Align with FDA recommended dosing
    b. Authorization Period: 2 months with the allowance of only one dose per lifetime
    c. Renewal Criteria: Not applicable as no further authorization will be provided

[a] Refractory (resistant) disease is defined as those patients who fail to obtain complete response with induction therapy, ie, 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).
[b] Relapsed disease describes the reappearance of leukemia cells in the bone marrow or peripheral blood after the attainment of a complete remission with chemotherapy and/or allogeneic stem cell transplant

***Note: Coverage may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Therapeutic considerations:

A. **FDA approved indication / Diagnosis**

**Please refer to most recent prescribing information.*

B. **Background Information**

a. CAR-T therapy is a type of treatment the utilizes the body's own immune system to fight cancer. T-cells are collected from the patient via apheresis and are genetically engineered in the laboratory to produce chimeric antigen receptors on the cell surface, allowing the T-cells to recognize an antigen on target cancer cells. Once the tumor cells are identified, they are attacked and killed by the CAR-T therapy.

b. CAR-T therapy has not been studied when given following prior treatment with any CAR-T therapy or following any other genetically-modified T-cell therapy.

c. Due to the risk of cytokine release syndrome and neurological toxicities, CAR-T therapies are only allowed to be given at treatment centers certified by their REMS programs. CAR-T REMS programs require certified hospitals and their clinics to have on-site, immediate access to tocilizumab and an understanding of how to manage the risks of the associated CAR-T side effects.

d. Kymriah is indicated for patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse. It is also approved for use in adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for treatment of patients with primary central nervous system lymphoma.

e. Safety and efficacy was established in two studies. The first was the ELIANA trial, an open-label, multicenter single-arm study of 107 pediatric and young adult patients with relapsed/refractory B-cell precursor ALL. All patients were screened, 88 were enrolled in the study, 68 were treated with CAR-T, and 63 were evaluable for efficacy. Nine percent of the enrolled subjects did not receive the product due to manufacturing failure. Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m2 daily for 4 days and cyclophosphamide 500 mg/m2 daily for 2 days) followed by a single dose of Kymriah. Tumors must have had CD19 expressing tumor cells. Patients were included if they were primary refractory defined as not achieving a complete response after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a complete response after 1 cycle of standard chemotherapy for relapsed leukemia; has Philadelphia chromosome positive (Ph+) ALL and were intolerant to or failed 2 lines of tyrosine kinase inhibitor therapy (TKI) or if TKI therapy was contraindicated; they were ineligible for allogeneic stem cell transplant (SCT); or had any bone marrow (BM) relapse after allogenic SCT. Patients were excluded if they had Burkitt's lymphoma, active hepatitis B or C, any uncontrolled infection, grade 2 to 4 graft-versus-host disease, concomitant genetic syndrome with the exception of Down's syndrome, or if they have received allogeneic cellular therapy, such as donor lymphocyte infusion within 6 weeks prior to Kymriah infusion. Efficacy was based on complete remission (CR) within 3 months after infusion, the duration of CR, and proportion of patients with CR and minimal residual disease (MRD) < 0.01% by flow cytometry (MRD-negative). Among the 63 infused patients, 52 (83%) achieved CR/CRi, all of which were MRD-negative. With a median follow-up of 4.8 months from response, the median duration of CR/CRi was not reached (range: 1.2 to 14.1+ months). Median time to onset of CR/CRi was 29 days with onset of CR/CRi between 26 and 31 days for 50/52 (96%) responders. The stem cell transplantation rate among those who achieved CR/CRi was 12% (6/52).

f. Efficacy was also established in the JULIET trial, an open-label, multicenter, single-arm trial of 160 adult patients with relapsed or refractory DLBCL, who received ≥ 2 lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous hematopoietic stem cell transplantation (HSCT). Of the160 patients enrolled, 106 patients received Kymriah. Eleven patients enrolled did not receive Kymriah due to manufacturing failure and 38 other patients did not receive Kymriah due to death (n = 16), physician decision (n = 16), or adverse events (n = 3). Patients with active central nervous system malignancy, prior allogenic HSCT, an ECOG performance status ≥ 2, a creatinine clearance < 60, alanine aminotransferase > 5 times normal, cardiac ejection fraction < 45%, or absolute lymphocyte concentration less than 300/µL were excluded from the study. The primary endpoints were complete response (CR) rate and duration of response (DOR). The median time to first response was 0.9 months (range: 0.7 to 3.3 months). The median duration of response was not reached. Response durations were longer in patients who achieved CR as compared to patients with a best response of partial response (PR). Of the 22 patients who

experienced a CR, 9 achieved this status by 1 month, 12 more by month 3, and the last by month 6 after Kymriah infusion.

g. Disease should be measured/staged with PET-CT. Focal uptake in nodal and extranodal sites is considered involvement with lymphoma, including spleen, liver, bone, thyroid, and so on. A measurable node must have a longest diameter (LDi) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

C. **Efficacy**

**Please refer to most recent prescribing information.*

D. **Medication Safety Considerations**

**Please refer to most recent prescribing information.*

E. **Dosing and administration**

**Please refer to most recent prescribing information.*

F. **How supplied**

**Please refer to most recent prescribing information.*

References:

1. Kymriah [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2021.
2. Clinicaltrials.gov. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in pediatric patients with relapsed and refractory b-cell acute lymphoblastic leukemia. Available at: https://clinicaltrials.gov/ct2/show/study/NCT02435849. Accessed on August 3, 2017.
3. LaRussa A. Chimeric antigen receptor (CAR) t-cell therapy. 10 Sept. 2015. Available at: www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy. Access on August 3, 2017.
4. National Comprehensive Cancer Network. Pediatric acute lymphoblastic leukemia (Version 2.2021). 2020 Oct 22. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed on June 18, 2021.
5. National Comprehensive Cancer Network. Acute lymphoblastic leukemia (Version 1.2021). 2021 April 6. Available at: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed on June 18, 2021.
6. National Comprehensive Cancer Network. B-cell lymphomas (Version 4.2021). 2021 May 5. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed on June 18, 2021.
7. Lee DW et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10; 124 (2): 188 - 195.
8. Clinicaltrials.gov. A phase II, single arm, multicenter trial to determine the efficacy and safety of CTL019 in adult patients with relapsed or refractory diffuse large b-cell lymphoma (DLBCL). Available at: https://clinicaltrials.gov/ct2/show/NCT02445248. Accessed on August 3, 2017.

Policy History		
#	Date	Change Description
1.0	Effective Date: 08/12/2021	New policy - this policy replaces previously approved criteria that was embedded in Chimeric Antigen Receptor-T Cell Class policy which will be retired

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*