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Subject: Tisagenlecleucel (Kymriah) Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Tisagenlecleucel (Kymriah) is a CD19-directed, genetically-modified autologous T cell immunotherapy that was first approved by the U.S. Food and Drug Administration (FDA) in August 2017 for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. The approval marked a historic moment being the first gene therapy and first chimeric antigen receptor (CAR) T-cell therapy approved by the FDA. Tisagenlecleucel was previously granted orphan designation by the FDA for the treatment of ALL in January 2014 and for the treatment of diffuse large B-cell lymphoma (DLBCL) in February 2015. In May 2018, the FDA-approved tisagenlecleucel for a second indication of "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". Axicabtagene ciloleucel (Yescarta) was the first CAR T-cell therapy to be FDA-approved for r/r large B-cell lymphoma in October 2017. Tisagenlecleucel works by reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and normal B cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of the tisagenlecleucel cells. Treatment involves removing, genetically modifying, and then re-infusing a patient's own T-cells. During the manufacturing process, a lentiviral vector encodes the CAR molecule via transduction; the vector enters the cell and becomes integrated into the chromosomes of T cells and directs transcription of the tisagenlecleucel CAR.

Acute lymphoblastic leukemia (ALL) is heterogenous hematological disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. The median age of diagnosis is 15 years with 57% of patients diagnosed at younger than 20 years of age. ALL represents 75 to 80% of acute leukemias among children, making it the most common form of

childhood leukemia. ALL is broadly classified in 3 groups based on immunophenotype, which include precursor B-cell ALL, mature B-cell ALL (a.k.a., Burkitt leukemia/lymphoma), and T-cell ALL. In children, B-cell lineage ALL constitutes about 88% of cases. Cure rates and survival outcomes have improved dramatically over the past several decades due to advances in understanding molecular genetics and pathogenesis of the disease, incorporation of risk-adapted therapy, and advent of new targeted agents. The 5-year overall survival (OS) rate for children is 86 to 89%. However, despite major advances in the treatment of childhood ALL, about 20% of pediatric patients experience relapse after an initial complete response (CR) to frontline treatment. Among those who experience relapse, only 30% experience long-term remission with subsequent therapies. The treatment of ALL represents one of the most complex and intensive program in cancer therapy. Treatment varies depending on subtype, age, and treatment history. In general, the treatment phases can be largely grouped into induction, consolidation, and maintenance. The National Comprehensive Cancer Network (NCCN) guidelines for ALL (Version 1.2018) list single-agent tisagenlecleucel therapy as a Category 2A recommendation for: (1) relapsed/refractory Ph+ B-ALL in patients <26 years and with refractory disease or ≥2 relapses and failure of 2 tyrosine kinase inhibitors (TKIs), and for (2) relapsed/refractory Ph- B-ALL in patients <26 years and with refractory disease or ≥2 relapses.

Diffuse large B-cell lymphomas are the most common lymphoid neoplasms in adults, and account for approximately 32.5% of non-Hodgkin lymphoma (NHLs) cases diagnosed annually. The DLBCLs exhibits large heterogeneity in morphologic, genetic, and clinical aspects. Multiple clinicopathologic entities are defined by the 2016 World Health Organization (WHO) classification, which are sufficiently distinct to be considered separate diagnostic categories. Adequate immunophenotyping is essential to establish the diagnosis, and to determine germinal center B-cell like (GCB) vs. non-GBC origin. Combination chemoimmunotherapy in the first-line setting (e.g., rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone [R-CHOP]) is associated with a 5-year survival rate ranging from 60% to 70%. Interim restaging should be performed to identify patients who disease has not responded to or has progressed on induction therapy. Based on a number of prognostic factors, 20% to 50% of DLBCL cases are refractory or relapse after first-line chemotherapy and the response rates to subsequent salvage chemotherapy and consolidation with autologous hematopoietic stem cell transplantation (HSCT) is suboptimal. The National Comprehensive Cancer Network (NCCN) B-cell Lymphoma Guidelines (Version14.2019) list tisagenlecleucel as a category 2A recommendation for the treatment of relapsed/refractory DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma [with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma), or not otherwise specified (NOS)], AIDS-related DLBCL, HHV8-positive DLBCL, NOS, and monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type) for patients with two or more disease relapses (if not previously given) or, for those patient with the intention to proceed to high-dose therapy, a non-complete response (i.e., partial response or worse) to second-line therapy. There is a footnote stating, “Tisagenlecleucel is not FDA-approved for relapsed/refractory primary mediastinal large B-cell lymphoma”. Tisagenlecleucel ciloleucel is also a 2A recommendation for the treatment of follicular lymphoma with histological transformation to DLBCL in patients with 2 or more prior chemotherapy regimens (with at least one being an anthracycline or anthracenedione-based regimen, unless contraindicated).

The safety and efficacy of tisagenlecleucel leading to FDA approval for ALL was evaluated in an open-label, multicenter, single-arm phase 2 trial (ELIANA) of pediatric and young adults with relapsed or refractory B-cell precursor ALL. A total of 107 patients were screened, 88 were enrolled, 68 were treated, and 63 were evaluable for efficacy. Eight subjects (9%) did not received treatment due to manufacturing failure. The 63 evaluable patients included 35 males and 28 females of median age 12 years (range, 3 to 23 years). Six (10%) had primary refractory disease, 30 (48%) had one prior stem cell transplantation,

and 5 patients (8%) had two stem cell transplantations. The median number of prior lines of therapy was 3 (range 1 to 8). Treatment consisted of lymphodepleting chemotherapy (fludarabine 30 mg/m^2 daily for 4 days and cyclophosphamide 500 mg/m^2 daily for 2 days) followed by a single dose of tisagenlecleucel. Of the 22 patients who had a WBC count less than 1,000/mcL, 20 received lymphodepleting chemotherapy prior to tisagenlecleucel while 2 received tisagenlecleucel infusion without lymphodepleting chemotherapy. Fifty-three patients received bridging chemotherapy between time of enrollment and lymphodepleting chemotherapy. Efficacy was established on the basis of complete remission (CR) or complete remission with incomplete blood count recovery (CRi) within 3 months after infusion, the duration of CR/CRi, and proportion of patients with CR/CRi and minimal residual disease (MRD)-negative (i.e., <0.01% by flow cytometry). 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). Adverse events (AEs) were common. The incidence of serious AEs within 8 weeks of infusion was 69%. Cytokine release syndrome (CRS occurred in 78% of patients (21% grade 3; 27% grade 4); no CRS-associated deaths occurred. Tocilizumab for treatment of CRS was given to 38% of patients. The most common grade 3 or 4 non-hematologic adverse events (>15%), other than CRS, were hypotension (22%), hypoxia (18%), and increased aspartate aminotransferase (16%). Grade 3 neuropsychiatric AEs occurred in 15% of patients, with no grade 4 events and no cerebral edema reported. Grade 3 or 4 neutropenia with high (>38.3˚C) fever occurred in 60% of patients.

The safety and efficacy of tisagenlecleucel leading to FDA approval for r/r DLBCL was evaluated in an open-label, multicenter, single-arm phase 2 trial (JULIET). The study included adult patients with r/r DLBCL who received 2 or more lines of chemotherapy, including rituximab and anthracycline, or relapsed following autologous HSCT. The study excluded patients with active CNS malignancy, prior allogenic HSCT, and an ECOG performance status of 2 or more. Bridging chemotherapy was permitted at investigator discretion to support patients with progressive disease while awaiting product manufacture. Patients were treated with an IV infusion of 1-5 x 10^8 viable tisagenlecleucel cells after lymphodepletion with cyclophosphamide/fludarabine or bendamustine if their WBC was ≥ 1x10^6 cells/mcL. The primary endpoint was the objective response rate (ORR) per the Lugano criteria [2014] defined as the sum of the percent complete responses and partial responses (% CR + %PR) at the time of best overall response. The durability of response, a key secondary endpoint, was assessed from time of initial response to time of relapse or last observation. Of the 92 patients receiving tisagenlecleucel, 90% received physician's choice of bridging chemotherapy in the interval between start of screening and tisagenlecleucel infusion. A retrospectively identified sub-group of 68 patients was evaluable for the major efficacy outcome measures. Among the efficacy evaluable population of 68 patients, the baseline characteristics were: median age 56 years (range: 22 to 74 years); 71% male;; 78% had primary DLBCL not otherwise specified (NOS) and 22% had DLBCL following transformation from follicular lymphoma, of whom 17% were identified as high grade; and 44% had undergone prior autologous HSCT. The median number of prior therapies was three (range: 1 to 6), 56% had refractory disease and 44% relapsed after their last therapy. Seventy-three percent (73%) of patients received tisagenlecleucel in the inpatient setting. The ORR was 50% (n=34, 95% CI 37.6 to 62.4%). Complete response was seen in 22 patients (32%) and partial response in 12 patients (18%). The median time to first response (CR or PR) 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). The most common adverse reactions were cytokine release syndrome (74%, Grade 3 or higher 23%), infections (42%, Grade 3 or higher 25%), diarrhea (31%), nausea (27%), pyrexia (34%), fatigue

(26%), hypotension (26%, Grade 3 or higher 8%), edema (23%), headache (21%), febrile neutropenia (17%), encephalopathy (16%, Grade 3 or higher 11%), and hypogammaglobulinemia (14%).

POSITION STATEMENT:

Initiation of tisagenlecleucel (Kymriah) **meets the definition of medical necessity** for members diagnosed with **EITHER** of the following conditions ("1" or "2"), and **ALL** associated criteria are met:

1. B-cell precursor acute lymphoblastic leukemia (ALL):
    a. The member will be less than or equal to 25 years of age at the time of the of the treatment infusion
    b. The member is positive for CD19 tumor expression in bone marrow or peripheral blood – confirmatory laboratory documentation must be submitted
    c. **EITHER** of the following ("i" or "ii"):
        i. Member has refractory disease defined as the inability to achieve a complete response (CR) at the end of induction chemotherapy
        ii. Member has experienced **TWO or more** disease relapses (after achieving CR) following recommended chemotherapies. For members with Ph+ ALL, treatment must have included at least two different tyrosine kinase inhibitors (TKIs) unless TKI use was contraindicated (the specific contraindication must be provided).
    d. The member will receive a lymphodepleting chemotherapy regimen (e.g., fludarabine and cyclophosphamide) to be completed 2 to 14 days prior to the administration of tisagenlecleucel, **OR** the treating physician attests that a lymphodepleting regimen is not appropriate due to profound leukopenia
    e. Following the completion of lymphodepleting chemotherapy (as needed), tisagenlecleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)
    f. Member has adequate organ and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist
    g. Tisagenlecleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation
    h. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including tisagenlecleucel) in their lifetime for the treatment of lymphoma or leukemia
    i. The healthcare facility where tisagenlecleucel is to be administered has enrolled in the Kymriah REMS program
    j. The dose of tisagenlecleucel will not exceed the following based on the member's body weight at the time of leukapheresis:
        - 50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg
        - Greater than 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based)
2. Large B-cell lymphoma:
    a. Member is 18 years of age or older at the time of the of the treatment infusion
    b. The members large B-cell lymphoma includes any of the following subtypes ("i" to "viii"- documentation of the lymph node biopsy results AND immunophenotyping and/or gene expression profiling results with interpretation confirming the diagnosis and specific subtype must be submitted:
        i. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)

ii. Primary mediastinal large B-cell lymphoma (PMBCL or PMBL)

iii. High-grade B-cell lymphoma (HGBL), with MYC and BCL2 and/or BCL6 translocations [a.k.a., double-hit or triple-hit lymphomas]

iv. High-grade B-cell lymphoma, NOS

v. DLBCL arising from follicular lymphoma [a.k.a., follicular lymphoma with histological transformation to DLBCL or transformed follicular lymphoma (TFL)]

vi. AIDS-related diffuse large B-cell lymphoma

vii. HHV8 (human herpesvirus 8)-positive diffuse large B-cell lymphoma, NOS

viii. Monomorphic post-transplant lymphoproliferative disorders (PTLD) (B-cell type)

c. Member has relapsed or refractory disease meeting **EITHER** of the following criteria ("i" or ii"):

i. Member was unable to achieve a complete response (CR) following their second line of systemic chemotherapy

ii. Member's disease is in second or greater relapse/recurrence

d. Member has received **TWO** or more unique lines of systemic chemotherapy for their disease (which may or may not include therapy supported by autologous stem cell transplant), **AND** prior therapy must have included an 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 – medical record documentation of the member's prior lines of therapy for their lymphoma must be submitted

e. Following the completion of lymphodepleting chemotherapy (as needed), tisagenlecleucel will be used as single-agent therapy (i.e., not used in combination with maintenance chemotherapy)

f. Member has adequate organ and bone marrow function with no significant deterioration expected within 4 weeks after apheresis as determined by the treating oncologist/hematologist

g. Tisagenlecleucel will not be administered if the member has an uncontrolled systemic infection at the time of planned treatment initiation

h. Member has **NOT** previously received CD19-directed chimeric antigen receptor (CAR) T-cell therapy (including tisagenlecleucel) in their lifetime for the treatment of lymphoma or leukemia

i. The healthcare facility where tisagenlecleucel is to be administered has enrolled in the Kymriah REMS program

j. The administration of tisagenlecleucel will not exceed one single dose as provided by the manufacturer

Approval duration: 3 months to allow for a one-time infusion of therapy

Tisagenlecleucel (Kymriah) is considered **experimental or investigational** for all other indications 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:

- Burkitt lymphoma/leukemia (i.e., patients with mature B-cell ALL)
- Castleman's disease
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Marginal zone lymphomas

- Non-B-cell lymphomas (e.g., T-cell lymphomas)
- Non-transformed follicular lymphoma
- Primary cutaneous B-cell lymphomas
- Primary DLBCL of the central nervous system (CNS)
- T-cell ALL

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- For the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
    - One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy followed by infusion of tisagenlecleucel.
        - For patients 50 kg or less: administer 0.2 to 5 x 10^6 CAR-positive viable T cells per kg body weight reported at the time of leukapheresis
        - For patients above 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based)
    - Lymphodepleting chemotherapy consists of fludarabine (30 mg/m^2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days starting with the first dose of fludarabine). Infuse tisagenlecleucel 2 to 14 days after completion of the lymphodepleting chemotherapy.
- For the 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 . Per the package labeling, "Limitation of Use: Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma".
    - One treatment course consists of fludarabine and cyclophosphamide lymphodepleting chemotherapy (or bendamustine as an alternative regimen) followed by infusion of tisagenlecleucel.
        - Administer 0.6 to 6 x 108 CAR-positive viable T cells (non-weight based)
    - Lymphodepleting chemotherapy consists of fludarabine (25 mg/m2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m2 intravenous daily for 3 days starting with the first dose of fludarabine). An alternate lymphodepleting chemotherapy of bendamustine 90 mg/m2 IV daily for 2 days can be used if a patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen .Lymphodepleting chemotherapy may be omitted if a patient's WBC count is less than or equal to 1 x 109/L within 1 week prior to the planned tisagenlecleucel infusion. Infuse tisagenlecleucel 2 to 11 days after completion of the lymphodepleting chemotherapy.
- Premedicate patients with acetaminophen and an H1-antihistamine. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of tisagenlecleucel. Tocilizumab (Actemra) and emergency equipment should be available prior to infusion and during the recovery

period. Consult the package labeling for specific directions on the preparation and administration of tisagenlecleucel.

Dose Adjustments

- Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.

Drug Availability

- Supplied as a frozen suspension of genetically modified autologous T cells in one or more infusion bags labeled for the specific recipient. Product is shipped directly to the cell lab associated with the infusion center in a liquid nitrogen Dewar. Product and patient-specific labels are located inside the Dewar. The product will have a difference NDC depending on the indication for use - Ped ALL: NDC 0078-0846-19 or DLBCL: NDC 0078-0958-19.
- Based on the patient's indication and weight reported at the time of leukapheresis, different dosages will be prepared for the patient:
  - DLBCL: 0.6 to 6.0 x 108 CAR-positive viable T cells
  - ALL (for patients 50 kg or less): 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
  - ALL (for patients above 50 kg): 0.1 to 2.5 x 10^8 CAR-positive viable T cells
- The actual number of CAR-positive T cells in the product is reported on the Certificate of Analysis (CoA) that is shipped with the product. The volume of CAR-positive viable T cells in an infusion bag ranges from 10 mL to 50 mL.

PRECAUTIONS:

Boxed Warning

WARNING: CYTOKINE RELEASE SYNDROME AND NEUROLOGICAL TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving tisagenlecleucel. Do not administer tisagenlecleucel to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with tisagenlecleucel, including concurrently with CRS. Monitor for neurological events after treatment with tisagenlecleucel. Provide supportive care as needed.
- Tisagenlecleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS.

Contraindications

- None

Precautions/Warnings

- **Cytokine Release Syndrome (CRS)**: CRS, including fatal or life-threatening reactions, occurred following treatment with tisagenlecleucel. In Study 1, CRS occurred in 79% (54/68) of patients, including Grade 3 or 4 (Penn grading system1) CRS in 49% (33/68) of patients. The median time to onset of CRS was 3 days (range: 1 to 22 days). Of the 54 patients with CRS, 27 (50%) received tocilizumab; 7 (13%) patients received two doses of tocilizumab, 3 (6%) patients received three doses of tocilizumab, and 14 (26%) patients received addition of corticosteroids (e.g., methylprednisolone). The median time to resolution of CRS was 8 days (range: 1 to 36 days). Key manifestations of CRS include high fever, lower than normal blood pressure, difficulty breathing, and may be associated with hepatic, renal, and cardiac dysfunction, and coagulopathy. Risk factors for severe CRS are high pre-infusion tumor burden (greater than 50% blasts in bone marrow), uncontrolled or accelerating tumor burden following lymphodepleting chemotherapy, active infections, and/or inflammatory processes. Ensure that tocilizumab is available on site prior to infusion. Monitor patients for signs or symptoms of CRS for at least 4 weeks after treatment. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care, tocilizumab and/or corticosteroids as indicated. Refer to the package labeling for detailed recommendation on the management of CRS.
- **Neurological Toxicities**: Neurological toxicities, which may be severe or life-threatening, can occur following treatment with tisagenlecleucel. The majority of neurological toxicities occurred within 8 weeks following infusion. In Study 1, neurological toxicities within 8 weeks occurred in 65% of patients, including Grade 3 or 4 neurological toxicities in 18% of patients, and the 75% of events resolved within 12 days. The most common neurological toxicities were headache (37%), encephalopathy (34%), delirium (21%), anxiety (13%), and tremor (9%). Other manifestations of neurological toxicities included disturbances in consciousness, disorientation, confusion, agitation, seizures, mutism and aphasia. Onset of neurological toxicity can be concurrent with CRS, following resolution of CRS or in the absence of CRS. Monitor patients for neurological events and exclude other causes for neurological symptoms. Provide supportive care as needed.
- **KYMRIAH REMS to Mitigate Cytokine Release Syndrome and Neurological Toxicities**: Because of the risk of CRS and neurological toxicities, tisagenlecleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the KYMRIAH REMS. The required components of the KYMRIAH REMS are: (1) Healthcare facilities that dispense and administer tisagenlecleucel must be enrolled and comply with the REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after tisagenlecleucel infusion, if needed for treatment of CRS. (2) Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer tisagenlecleucel are trained about the management of CRS and neurological toxicities.
- **Hypersensitivity Reactions**: Monitor for hypersensitivity reactions during infusion. Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) or dextran 40.
- **Serious Infections**: Serious infections, including life-threatening or fatal infections, occurred in patients after infusion. In Study 1, infections (all Grades) after tisagenlecleucel infusion occurred in 40 patients (59%), including 24 patients (35%) with Grade 3-4 infections and 2 patients (3%) with fatal infections. Infections with an unknown pathogen occurred in 41% of patients, viral infections in 26%, bacterial infections in 19%, and fungal infections in 13%. Prior to tisagenlecleucel infusion, infection prophylaxis should follow local guidelines. Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged Cytopenias**: Patients may exhibit cytopenias for several weeks following tisagenlecleucel infusion. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly GM-CSF, are not recommended during the first 3 weeks after tisagenlecleucel infusion or until CRS has resolved.

- **Hypogammaglobulinemia**: Hypogammaglobulinemia and agammaglobulinemia (IgG) related to B-cell aplasia can occur in patients with a complete remission (CR) after infusion. Hypogammaglobulinemia was reported in 43% of patients treated with tisagenlecleucel for r/r ALL and 14% of patients with r/r DLBCL. Monitor and provide replacement therapy until resolution. Assess immunoglobulin levels in newborns of mothers treated with tisagenlecleucel.
- **Secondary Malignancies**: Patients treated with tisagenlecleucel may develop secondary malignancies or recurrence of their leukemia. Monitor life-long for secondary malignancies In the event that a secondary malignancy occurs after treatment with tisagenlecleucel, contact Novartis Pharmaceuticals Corporation at 1-844-4KYMRIAH.
- **Effects on Ability to Drive and Use Machines**: Due to the potential for neurological events, including altered mental status or seizures, patients receiving tisagenlecleucel are at risk for altered or decreased consciousness or coordination. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving tisagenlecleucel.
- **HIV Testing**: HIV and the lentivirus used to make tisagenlecleucel have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NAT) tests may yield false-positive results in patients who have received tisagenlecleucel.
- **Prenancy**: There are no available data with use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted and it is not known if tisagenlecleucel has the potential to be transferred to the fetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia. Therefore, tisagenlecleucel is not recommended for women who are pregnant.

BILLING/CODING INFORMATION:

The collection of leukapheresis provides the starting material for the manufacturing of tisagenlecleucel and should **NOT** be billed separately.

HCPCS Coding

Q2042	Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

ICD-10 Diagnoses Codes That Support Medical Necessity

C83.30 - C83.39	Diffuse large B-cell lymphoma
C85.10 - C85.19	Unspecified B-cell lymphoma
C85.20 - C85.29	Mediastinal (thymic) large B-cell lymphoma
C85.80 - C85.89	Other specified types of non-Hodgkin lymphoma
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, in relapse
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of guideline creation.

DEFINITIONS:

Autologous: Cells or tissues obtained from the same individual (as opposed to from a different person).

CD19: Cluster of Differentiation 19 is a protein found on the surface of B-cells in humans. Fully differentiated plasma cells no longer express CD19.

Chimeric antigen receptor (CAR) T-cell therapy: A type of treatment in which a patient's T cells are changed in the laboratory so they will attack cancer cells. T cells are taken from a patient's blood. Then the gene for a special receptor that binds to a certain protein on the patient's cancer cells is added in the laboratory. The special receptor is called a chimeric antigen receptor (CAR). Large numbers of the CAR T cells are grown in the laboratory and given to the patient by infusion.

Complete response (CR) (in ALL): (1) no circulating blast or extramedullary disease including no lymphadenopathy, splenomegaly, skin/gum infiltration, testicular mass, or CNS involvement (2) trilineage hematopoiesis (TLH) and <5% blasts, (3) absolute neutrophil count (ANC) >1,000/mcL, (4) platelets >100,000/mcL, and (5) no recurrence for 4 weeks

Complete response with incomplete blood count recovery (CRi) (in ALL): Same criteria for CR except platelet count and/or ANC.

Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS): The 2008 WHO classification of mature B-cell lymphomas included DLBCL, NOS as a new category to include germinal center B-cell (GCB) subtype, activated B-cell (ABC) subtype as well as other DLBCL cases that do not belong to any of the four specific subtypes (T-cell/histiocyte rich large B-cell lymphoma, primary CNS DLBCL, primary cutaneus DLBCL ("leg type"), or EBV+ DLBCL of the elderly). The updated 2016 WHO classification system created additional categories that fall outside of the definition of DLBCL, NOS.

Gene therapy: The therapeutic delivery of nucleic acid polymers into a patient's cells as a drug to treat disease.

Leukapheresis: A laboratory procedure in which white blood cells (WBC) are separated from a sample of blood. It is a specific type of apheresis, the more general term for separating out one particular constituent of blood and returning the remainder to the circulation. It is the first step in CAR T-cell therapy.

Minimal Residual Disease (MRD): The presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone morrow. There is a strong correlation between MRD and risk for relapse. Current methods for MDR assessment include multicolor flow cytometry assays specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative PCR assays, and next-generation sequencing-based assays. Current multicolor flow cytometry or PCR methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells.

Primary mediastinal large B-cell lymphoma (PMBL): A distinct subtype of NHL presenting with primary site of disease in the mediastinum with or without other site and has histology of DLBCL. It tends to occur in young adults with a median age of 35 years with a slight female predominance.

Progressive ALL: Increase of at least 25% in the absolute number of circulating or bone marrow blasts or the development of extramedullary disease.

Refractory ALL: Failure to achieve a CR at the end of induction therapy.

Relapsed ALL: Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR.

RELATED GUIDELINES:

Adoptive Immunotherapy, 01-96400-01

Axicabtagene Ciloleucel (Yescarta), 09-J2000-95

OTHER:

Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
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 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

International Working Group (IWG) Response Criteria for Malignant Lymphoma

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
Complete remission	Disappearance of all	(a) FDG-avid or PET positive prior to therapy; mass of any size	Not palpable, nodules	Infiltrate cleared on repeat

(CR)	evidence of disease	permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	disappeared	biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
Partial remission (PR)	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	
Stable disease (SD)	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or progressive disease (PD)	Any new lesion or increase by ≥50% of previously involved sites from nadir	Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
FDG - [^{18}F]fluorodeoxyglucose; PET - positron emission tomography; CT - computed tomography; SPD - sum of the product of the diameters				

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/09/19.

GUIDELINE UPDATE INFORMATION:

11/15/17	New Medical Coverage Guideline.
01/01/18	Annual HCPCS coding update: added HCPCS code Q2040.
03/05/18	Revision; Updates to Billing/Coding Information section.
07/15/18	Revision to guidelines consisting updates to the description section, position statement, dosage/administration section, precautions section, billing/coding information, definitions, and references based on the new FDA-approved indication for r/r DLBCL and updated NCCN B-Cell Lymphoma guidelines.
01/01/19	Revision: HCPCS code updates. Added Q2042, and removed Q2040.
02/15/19	Review and revision of guidelines consisting of updating the description, position statement, billing/coding, related guidelines, and references.