 Approved Revision: Do Not Implement Until 4/2/21

Tisagenlecleucel

NDC CODE(S) 00078-0846-XX KYMRIAH Suspension (NOVARTIS)
00078-0958-XX KYMRIAH Suspension (NOVARTIS)

DESCRIPTION

Tisagenlecleucel (Kymriah®) is a CD19-directed genetically modified autologous T cell immunotherapy. Each dose is a customized treatment created using an individual's own T-cells. The individual's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the individual. Upon binding to the CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination and persistence of the tisagenlecleucel cells.

POLICY

- Tisagenlecleucel for the treatment of B-cell Precursor Acute Lymphoblastic Leukemia (ALL) and Large B-Cell Lymphoma is considered ***medically necessary*** if the medical appropriateness criteria are met. **(See Medical Appropriateness below.)**
- Tisagenlecleucel for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL

- Submission of medical records related to the medical necessity criteria is **REQUIRED** on all requests for authorizations. Records will be reviewed at the time of submission. Please provide documentation via direct upload through the PA web portal or by fax.
- Tisagenlecleucel is considered **medically appropriate** if **ALL** of the following criteria are met:
  - Individual is/has **ALL** of the following:
    - Free from active infection or inflammatory disorder including screening for **ALL** of the following in accordance with clinical guidelines prior to collection of cells (leukapheresis):
      - Hepatitis B virus (HBV)
      - Hepatitis C virus (HCV)
      - Human Immunodeficiency virus (HIV)
    - Life expectancy greater than 12 weeks
    - **NOT** received prior CAR-T therapy
    - **NOT** received prior anti-CD19 therapy, e.g., blinatumomab, etc., or previously received anti-CD19 therapy and re-biopsy indicates CD-19 positive disease
    - **NOT** received live vaccines within six weeks prior to initiation of lymphodepleting chemotherapy and will not receive live vaccines until immune recovery following tisagenlecleucel treatment
  - Prophylaxis for infection has been followed according to local guidelines
  - Healthcare facility has enrolled in the Kymriah REMS and training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities
  - Used as single agent therapy (not applicable to lymphodepleting or bridging chemotherapy)
  - Diagnosis of **ANY ONE** of the following:
    - B-Cell Precursor Acute Lymphoblastic Leukemia (ALL) if **ALL** of the following:
      - Individual is 3 to 25 years of age
      - Disease is refractory or in second or later relapse as exhibited by **ANY ONE** of the following:
        - Second or greater bone marrow relapse

- Any bone marrow relapse after allogeneic stem cell transplantation
- Primary refractory (not achieving a complete response after 2 cycles of standard chemotherapy)
- Chemorefractory (not achieving a complete response after 1 cycle of standard chemotherapy for relapsed disease)
- Individuals with Philadelphia chromosome positive (Ph+) disease have a contraindication, intolerance or have failed two prior lines of tyrosine kinase inhibitor therapy (e.g., imatinib, dasatinib, ponatinib)
- Individual is not eligible for allogeneic stem cell transplantation

- Individual has performance status (Karnofsky/Lansky) is greater than or equal to (≥) 50

- Large B-Cell Lymphoma if **ALL** of the following:
  - Individual is 18 years of age or older
  - ECOG performance status of 0-1
  - Individual does **NOT** have diagnosis of primary central nervous system lymphoma
  - Disease is relapsed or refractory
  - Diagnosis of **ANY ONE** of the following:
    - Diffuse large B-cell lymphoma (DLBCL) as histologic transformation for **ANY ONE** of the following:
      - Follicular Lymphoma (FL) or Nodal Marginal Zone Lymphoma if received **ALL** of the following:
        - Two or more prior lines of chemoimmunotherapy which must have included an anthracycline or anthracenedione-based regimen, unless contraindicated
        - Multiple lines of prior therapies for indolent or transformed disease
      - Follicular Lymphoma (FL) after minimal or no chemotherapy prior to histologic transformation and had partial response, no response, or progressive disease after treatment
    - Richter's transformation of CLL to DLBCL if **ANY ONE** of the following:
      - Received two or more prior lines of systemic therapy
      - Used for treatment of disease that is in second or greater relapse
    - High grade B-cell lymphoma, Diffuse Large B-cell Lymphoma, AIDS-Related Diffuse Large B-Cell Lymphoma, Primary Effusion Lymphoma, Primary Mediastinal Large B-cell Lymphoma (PMBCL), HHV8-positive diffuse large B-cell lymphoma, not otherwise specified or Monomorphic Post-Transplant Lymphoproliferative Disorder (B-cell type) if used as **ANY ONE** of the following:
      - Additional therapy for individual with intention to proceed to transplant with a partial response following second-line therapy for relapsed or refractory disease
      - Treatment of disease that is in second or greater relapse

RENEWAL CRITERIA

- Tisagenlecleucel is **NOT** considered **medically appropriate** for renewal

INDICATION(S)	DOSAGE & ADMINISTRATION
B-Cell Precursor Acute lymphoblastic leukemia	Lymphodepleting chemotherapy: • Fludarabine (30 mg/m2 intravenous daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenous daily for 2 days starting with the first dose of fludarabine). Kymriah Infusion: • Infuse 2 to 14 days after completion of lymphodepleting chemotherapy • KYMRIAH is provided in a single-dose unit containing chimeric antigen receptor (CAR)-positive viable T cells* based on the patient weight reported at the time of leukapheresis:

	○ For individuals ≤ 50 kg: administer 0.2 to 5.0 x 106 CAR-positive viable T cells per kg body weight ○ For individuals > 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells
Large B-cell Lymphoma	Lymphodepleting chemotherapy *(lymphodepleting chemotherapy may be omitted if an individual's white blood cell [WBC] count is less than or equal to 1 x 10^9/L within 1 week prior to Kymriah infusion)* with **ANY ONE** of the following: • 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) • Bendamustine (90 mg/m2 intravenous daily for 2 days) if the individual experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen Kymriah Infusion: • Infuse 2 to 11 days after completion of lymphodepleting chemotherapy • Kymriah is provided in a single-dose unit containing chimeric antigen receptor (CAR) -positive viable T cells* based on the individual weight reported at the time of leukapheresis: ○ Administer 0.6 to 6.0 x 10^8 CAR-positive viable T cells
For autologous use only. For intravenous use only. • Kymriah is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure • One treatment course consists of lymphodepleting chemotherapy followed by a single infusion of Kymriah • Confirm availability of Kymriah prior to starting the lymphodepleting regimen. • Delay the infusion of Kymriah after lymphodepleting chemotherapy for unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension), active uncontrolled infection, active graft versus host disease (GVHD), or worsening of leukemia burden.	
*See the Certificate of Analysis (CoA) for the actual number of chimeric antigen receptor (CAR)-positive T cells in the product	
• Store infusion bag in the vapor phase of liquid nitrogen (less than or equal to minus 120°C) in a temperature-monitored system. Thaw prior to infusion.	
• In case of manufacturing failure, a second manufacturing may be attempted.	
• Additional bridging chemotherapy may be necessary between leukapheresis and lymphodepleting chemotherapy	
• Tocilizumab must be available on site prior to infusion if needed for the treatment of CRS (2 doses minimum)	
• Biosafety guidelines must be followed. Product contains human cells genetically modified with a lentivirus. Employ universal precautions when handling	

LENGTH OF AUTHORIZATION

Coverage will be provided for one treatment course (1 dose) and may not be renewed

Click here to view **DOSAGE LIMITS**

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with **Tennessee** Code Annotated **Section 56-7-2352** regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the Medical Policy and a health plan, the express terms of the health plan will govern.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

SOURCES

Lemal, R., Tournilhac, O. (2019). State-of-the-art for CAR T-cell therapy for chronic lymphocytic leukemia in 2019. *Journal for ImmunoTherapy of Cancer,* 7(202), 1-6. Retrieved February 24, 2020 from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6676603/.

Maude, S. L., Laetsch, T.W., Buechner, J. Rives, S., Boyer, M., Bittencourt, H., et al. (2018). Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *The New England Journal of Medicine,* 378 (5), 439-448.

MICROMEDEX Healthcare Series. Drugdex Evaluations. (2020, September). *Tisagenlecleucel.* Retrieved November 20, 2020 from MICROMEDEX Healthcare Series.

National Comprehensive Cancer Network. (2020). NCCN Drugs & Biologics Compendium®. *Tisagenlecleucel.* Retrieved November 20, 2020 from the National Comprehensive Cancer Network.

U. S. Food and Drug Administration. (2018, May). Center for Vaccines, Blood and Biologics. *Kymriah™ (tisagenlecleucel)*. Retrieved November 20, 2020 from https://www.fda.gov/media/107296/download.

EFFECTIVE DATE 4/2/2021

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