MEDICA®

Kymriah® (tisagenlecleucel)
(Intravenous)

Document Number: MH-0319

Last Review Date: 10/22/2021
Date of Origin: 09/19/2017
Dates Reviewed: 09/2017, 06/2018, 11/2018, 10/2019, 12/2019, 11/2020, 11/2021
Customization Dates: 04/01/2022
Effective Dates: 04/01/2022

I. Length of Authorization

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

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- 1 infusion bag of up to 600 million CAR-positive viable T-cells

B. Max Units (per dose and over time) [HCPCS Unit]:

- 1 billable unit (1 infusion of up to 600 million CAR-positive viable T-cells)

III. Initial Approval Criteria [1-13]

Coverage is provided in the following conditions:

Submission of medical records (chart notes) 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 related to diagnosis, step therapy, and clinical markers (i.e. genetic and mutational testing) supporting initiation when applicable. Medical records may be submitted via direct upload through the PA web portal or by fax.

- Patient does not have an active infection or inflammatory disorder; **AND**
- Patient has not received live vaccines within 6 weeks prior to the start of lymphodepleting chemotherapy, and will not receive live vaccines during tisagenlecleucel treatment and until immune recovery following treatment; **AND**

Magellan Rx MANAGEMENT℠

- Patient has been screened for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in accordance with clinical guidelines prior to collection of cells (leukapheresis); **AND**
- Prophylaxis for infection will be followed according to local guidelines; **AND**
- 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; **AND**
- Patient has not received prior CAR-T therapy; **AND**
- Patient has not received prior anti-CD19 therapy, (e.g., blinatumomab, etc.) OR patient previously received anti-CD19 therapy and re-biopsy indicates CD-19 positive disease; **AND**
- Used as single agent therapy (not applicable to lymphodepleting or bridging chemotherapy); **AND**

Adult B-Cell Precursor Acute Lymphoblastic Leukemia (ALL) † Φ [1,8,10-13]

- Patient is 18 to 25 years of age; **AND**
- Patient has a performance status (Karnofsky/Lansky) ≥ 50; **AND**
    - Patient has Philadelphia chromosome (Ph)-positive disease; **AND**
        - Patient has refractory disease; **OR**
        - Disease is in second or greater relapse with failure of two (2) tyrosine kinase inhibitors (e.g., dasatinib, imatinib, ponatinib, nilotinib, bosutinib, etc.); **OR**
    - Patient has Philadelphia chromosome (Ph)-negative disease; **AND**
        - Disease is refractory or in second or later relapse

Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia (ALL) † Φ [1,8,10-13]

- Patient is 2 to 17 years of age; **AND**
- Patient has a performance status (Karnofsky/Lansky) ≥ 50; **AND**
    - Patient has Philadelphia chromosome (Ph)-positive disease; **AND**
        - Disease is tyrosine kinase inhibitor (TKI) intolerant or refractory; **OR**
        - Patient has relapsed disease post-hematopoietic stem cell transplant (HSCT); **OR**
    - Patient has Philadelphia chromosome (Ph)-negative disease; **AND**
        - Disease is refractory or in second or later relapse

B-Cell Lymphomas † ‡ Φ [1,3,8,9,14]

- Patient is at least 18 years of age; **AND**
- Patient has an ECOG performance status of 0-1; **AND**
- Patient does not have primary central nervous system lymphoma; **AND**
    - Patient has histologic transformation of follicular lymphoma or nodal marginal zone lymphoma to diffuse large B-cell lymphoma (DLBCL) OR Richter's transformation of CLL to DLBCL; **AND**

- Patient received at least two (2) prior lines of chemoimmunotherapy which must have included an anthracycline or anthracenedione-based regimen, unless contraindicated; **OR**

- Patient has diffuse large B-cell lymphoma, AIDS-related B-cell lymphoma (e.g., diffuse large B-cell lymphoma, primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma, not otherwise specified), high-grade B-cell lymphomas, or monomorphic post-transplant lymphoproliferative disorder (B-cell type); **AND**
  - Used as additional therapy for patients with intention to proceed to transplant who have a partial response following second-line therapy for relapsed or refractory disease; **OR**
  - Used for treatment of disease that is in second or greater relapse

† FDA Approved Indication(s); ‡ Compendium Recommended Indication(s); Φ Orphan Drug

IV. Renewal Criteria

Coverage cannot be renewed.

V. Dosage/Administration [1]

Indication	Dose
B-Cell Precursor ALL	<u>Lymphodepleting chemotherapy:</u> • Administer 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). <u>Kymriah Infusion:</u> • 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: • Patients ≤ 50 kg: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight • Patients > 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells
B-cell Lymphomas	<u>Lymphodepleting chemotherapy *(lymphodepleting chemotherapy may be omitted if a patient's white blood cell [WBC] count is less than or equal to 1 x 10^9/L within 1 week prior to Kymriah infusion)*:</u> • Administer fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine); **OR** • Administer bendamustine (90 mg/m^2 intravenous daily for 2 days) if the patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen <u>Kymriah infusion:</u> • 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 patient 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 Kymriah availability prior to starting the lymphodepleting regimen.
- Confirm the patient's identity with the patient identifiers on each KYMRIAH infusion bag(s).
- 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.

Premedication:

- Premedicate with acetaminophen and diphenhydramine (or another H1-antihistamine) 30-60 minutes prior to infusion. Avoid prophylactic system corticosteroids which may interfere with Kymriah activity.

Monitoring after infusion:

- Monitor patients 2-3 times during the first week following KYMRIAH infusion at the certified healthcare facility for signs and symptoms of CRS and neurologic toxicities.
- Instruct patients to remain within proximity of the certified healthcare facility for at least 4 weeks following infusion.
- Instruct patients to refrain from driving or hazardous activities for at least 8 weeks following infusion.

*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.

VI. Billing Code/Availability Information

HCPCS Code:

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

NDC(s):

- Kymriah suspension for intravenous infusion (Ped ALL); 1 infusion bag (10 to 50 mL): 00078-0846-xx
- Kymriah suspension for intravenous infusion (DLBCL); 1 infusion bag (10 to 50 mL): 00078-0958-xx

VII. References

1. Kymriah [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corp., August 2021. Accessed October 2021.
2. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med. 2015 Sep 2;7(303):303ra139. doi: 10.1126/scitranslmed.aac5415.
3. Schuster S, Bishop MR, Constantine T, et al. Global Pivotal Phase 2 Trial of the CD19-Targeted Therapy CTL019 In Adult Patients with Relapsed or Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL)—An Interim Analysis. Clinical Lymphoma, Myeloma and Leukemia, Volume 17, S373 - S374.
4. Mejstrikova E, Hrusak O, Borowitz MJ, et al. CD19-negative relapse of pediatric B-cell precursor acute lymphoblastic leukemia following blinatumomab treatment. Blood Cancer J. 20177; 659. DOI 10.1038/s41408-017-0023-x
5. Ruella M, Maus MV. Catch me if you can: Leukemia Escape after CD19-Directed T Cell Immunotherapies. Computational and Structural Biotechnology Journal 14 (2016) 357–362.
6. Braig F, Brandt A, Goebeler M, et al. Resistance to anti-CD19/CD3 BiTE in acute lymphoblastic leukemia may be mediated by disrupted CD19 membrane trafficking. Blood; 129:1, 2017 Jan.
7. Majzner RG, Mackall CL. Tumor Antigen Escape from CAR T-cell Therapy. *Cancer Discov* 2018;8:1219-1226.
8. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) tisagenlecleucel. National Comprehensive Cancer Network, 2021. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed October 2021.
9. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56. doi:10.1056/NEJMoa1804980.
10. Lee DW, Kochenderfer JN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2015;385(9967):517-528.
11. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014;371(16):1507-1517.
12. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. N Engl J Med. 2018;378(5):439-448.
13. Fitzgerald JC, Weiss SL, Maude SL, et al. Cytokine release syndrome after chimeric antigen receptor T cell therapy for acute lymphoblastic leukemia. Crit Care Med. 2017;45(2):e124-e131.

14. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 1.2022. National Comprehensive Cancer Network, 2021. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed October 2021.

Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C83.00	Small cell B-cell lymphoma, unspecified site
C83.01	Small cell B-cell lymphoma, lymph nodes of head, face and neck
C83.02	Small cell B-cell lymphoma, intrathoracic lymph nodes
C83.03	small cell B-cell lymphoma, intra-abdominal lymph nodes
C83.04	Small cell B-cell lymphoma, lymph nodes of axilla and upper limb
C83.05	Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.06	Small cell B-cell lymphoma, intrapelvic lymph nodes
C83.07	Small cell B-cell lymphoma, spleen
C83.08	Small cell B-cell lymphoma, lymph nodes of multiple sites
C83.09	Small cell B-cell lymphoma, extranodal and solid organ sites
C83.30	Diffuse large B-cell lymphoma unspecified site
C83.31	Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck
C83.32	Diffuse large B-cell lymphoma intrathoracic lymph nodes
C83.33	Diffuse large B-cell lymphoma intra-abdominal lymph nodes
C83.34	Diffuse large B-cell lymphoma lymph nodes of axilla and upper limb
C83.35	Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb
C83.36	Diffuse large B-cell lymphoma intrapelvic lymph nodes
C83.37	Diffuse large B-cell lymphoma, spleen
C83.38	Diffuse large B-cell lymphoma lymph nodes of multiple sites
C83.39	Diffuse large B-cell lymphoma extranodal and solid organ sites
C83.50	Lymphoblastic (diffuse) lymphoma, unspecified site
C83.51	Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck
C83.52	Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes
C83.53	Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes
C83.54	Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb
C83.55	Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb
C83.56	Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes

C83.57	Lymphoblastic (diffuse) lymphoma, spleen
C83.58	Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites
C83.59	Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites
C83.80	Other non-follicular lymphoma, unspecified site
C83.81	Other non-follicular lymphoma, lymph nodes of head, face and neck
C83.82	Other non-follicular lymphoma, intrathoracic lymph nodes
C83.83	Other non-follicular lymphoma, intra-abdominal lymph nodes
C83.84	Other non-follicular lymphoma, lymph nodes of axilla and upper limb
C83.85	Other non-follicular lymphoma, lymph nodes of inguinal region and lower limb
C83.86	Other non-follicular lymphoma, intrapelvic lymph nodes
C83.87	Other non-follicular lymphoma, spleen
C83.88	Other non-follicular lymphoma, lymph nodes of multiple sites
C83.89	Other non-follicular lymphoma, extranodal and solid organ sites
C83.90	Non-follicular (diffuse) lymphoma, unspecified site
C83.91	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of head, face, and neck
C83.92	Non-follicular (diffuse) lymphoma, unspecified intrathoracic lymph nodes
C83.93	Non-follicular (diffuse) lymphoma, unspecified intra-abdominal lymph nodes
C83.94	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of axilla and upper limb
C83.95	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of inguinal region and lower limb
C83.96	Non-follicular (diffuse) lymphoma, unspecified intrapelvic lymph nodes
C83.97	Non-follicular (diffuse) lymphoma, unspecified spleen
C83.98	Non-follicular (diffuse) lymphoma, unspecified lymph nodes of multiple sites
C83.99	Non-follicular (diffuse) lymphoma, unspecified extranodal and solid organ sites
C85.10	Unspecified B-cell lymphoma, unspecified site
C85.11	Unspecified B-cell lymphoma, lymph nodes of head, face, and neck
C85.12	Unspecified B-cell lymphoma, intrathoracic lymph nodes
C85.13	Unspecified B-cell lymphoma, intra-abdominal lymph nodes
C85.14	Unspecified B-cell lymphoma, lymph nodes of axilla and upper limb
C85.15	Unspecified B-cell lymphoma, lymph nodes of inguinal region and lower limb
C85.16	Unspecified B-cell lymphoma, intrapelvic lymph nodes
C85.17	Unspecified B-cell lymphoma, spleen
C85.18	Unspecified B-cell lymphoma, lymph nodes of multiple sites
C85.19	Unspecified B-cell lymphoma, extranodal and solid organ sites
C85.20	Mediastinal (thymic) large B-cell lymphoma unspecified site
C85.21	Mediastinal (thymic) large B-cell lymphoma lymph nodes of head, face, and neck
C85.22	Mediastinal (thymic) large B-cell lymphoma intrathoracic lymph nodes

C85.23	Mediastinal (thymic) large B-cell lymphoma intra-abdominal lymph nodes
C85.24	Mediastinal (thymic) large B-cell lymphoma lymph nodes of axilla and upper limb
C85.25	Mediastinal (thymic) large B-cell lymphoma lymph nodes of inguinal region and lower limb
C85.26	Mediastinal (thymic) large B-cell lymphoma intrapelvic lymph nodes
C85.27	Mediastinal (thymic) large B-cell lymphoma spleen
C85.28	Mediastinal (thymic) large B-cell lymphoma lymph nodes of multiple sites
C85.29	Mediastinal (thymic) large B-cell lymphoma extranodal and solid organ sites
C85.80	Other specified types of non-Hodgkin lymphoma, unspecified site
C85.81	Other specified types of non-Hodgkin lymphoma, lymph nodes of head, face and neck
C85.82	Other specified types of non-Hodgkin lymphoma, intrathoracic lymph nodes
C85.83	Other specified types of non-Hodgkin lymphoma, intra-abdominal lymph nodes
C85.84	Other specified types of non-Hodgkin lymphoma, lymph nodes of axilla and upper limb
C85.85	Other specified types of non-Hodgkin lymphoma, lymph nodes of inguinal region of lower limb
C85.86	Other specified types of non-Hodgkin lymphoma, intrapelvic lymph nodes
C85.87	Other specified types of non-Hodgkin lymphoma, spleen
C85.88	Other specified types of non-Hodgkin lymphoma, lymph nodes of multiple sites
C85.89	Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse
C91.10	Chronic lymphocytic leukemia of B-cell type not having achieved remission
C91.12	Chronic lymphocytic leukemia of B-cell type in relapse
D47.Z1	Post-transplant lymphoproliferative disorder (PTLD)

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC