Kymriah™ (tisagenlecleucel)
(Intravenous)

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Document Number: IC-0452

Last Review Date: 12/01/2020
Date of Origin: 05/01/2019
Dates Reviewed: 05/2019, 12/2019, 12/2020

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

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

B-Cell Precursor Acute Lymphoblastic Leukemia (ALL)
- 1 billable unit (1 infusion of up to 600 million car-positive viable t-cells)

Large B-Cell Lymphoma
- 1 billable unit (1 infusion of up to 600 million car-positive viable t-cells)

III. Initial Approval Criteria[1-13]

- 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.

Coverage is provided in the following conditions:

- 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 until immune recovery following Kymriah treatment; **AND**
- 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 has been 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**
- Patient has a life expectancy > 12 weeks; **AND**

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

- Patient aged 3 to 25 years; **AND**
- Patient's disease is refractory or in second or later relapse defined as one of the following:
    - Second or greater bone marrow (BM) relapse; **OR**
    - Any BM relapse after allogeneic stem cell transplantation (SCT); **OR**
    - Primary refractory (not achieving a complete response after 2 cycles of standard chemotherapy) or chemorefractory (not achieving a complete response after 1 cycle of standard chemotherapy for relapsed disease); **OR**
    - Patients with Philadelphia chromosome (Ph)-positive disease have a contraindication, intolerance, or have failed two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib, etc.); **OR**
    - Patient is not eligible for allogeneic SCT; **AND**
- Patient has a performance status (Karnofsky/Lansky) ≥ 50

Large B-Cell Lymphoma † Φ [3,8,9]

- Patient aged 18 years or greater; **AND**
- Patient has an ECOG performance status of 0-1; **AND**
- Patient does not have primary central nervous system lymphoma; **AND**
- Patient's disease is relapsed or refractory; **AND**
    - Patient has Diffuse large B-cell lymphoma (DLBCL) as histologic transformation; **AND**
        - Patient received two or more prior lines of chemoimmunotherapy which must have included an anthracycline and rituximab, unless contraindicated; **AND**
        - Patient had Follicular Lymphoma (FL); **AND**
            - Patient received multiple line of prior therapies for indolent or transformed disease; **OR**
        - Patient had Follicular Lymphoma (FL); **AND**
            - Patient received minimal or no chemotherapy prior to histologic transformation and had partial response, no response, or progressive disease after treatment; **OR**
    - Patient has DLBCL or high grade B-cell lymphoma; **AND**
        - Patient received two or more prior lines of systemic therapy which must have included an anthracycline and rituximab, unless contraindicated

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

† FDA Approved Indication(s); ‡ Compendium Recommended Indication(s)

IV. Renewal Criteria

Coverage cannot be renewed.

V. Dosage/Administration

Indication	Dose
B-Cell Precursor ALL	Lymphodepleting chemotherapy: • 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). 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: o Patients ≤ 50 kg: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight o Patients > 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 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)*: • 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** • 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 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 patient weight reported at the time of leukapheresis: o 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.

VI. Billing Code/Availability Information

Jcode:

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

NDC:

- 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 (STANDARD)

1. Kymriah [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corp., May 2018. Accessed October 2020.
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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
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VIII. References (ENHANCED)

1e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Acute Lymphoblastic Leukemia, Version 1.2020. National Comprehensive Cancer Network, 2020. 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 NCCN Guidelines, go online to NCCN.org. Accessed October 2020.

2e. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Pediatric Acute Lymphoblastic Leukemia, Version 1.2021. National Comprehensive Cancer Network, 2020. 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 NCCN Guidelines, go online to NCCN.org. Accessed October 2020.

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
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
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
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.02	Acute lymphoblastic leukemia, in relapse

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) and Local Coverage Determinations (LCDs) may exist and compliance with these policies is required where applicable. They can be found at: http://www.cms.gov/medicare-coverage-database/search/advanced-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): 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
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

Appendix 3 – CLINICAL LITERATURE REVIEW

OS = overall survival; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DOR = duration of response; TTP = time to progression; FFS = failure-free survival; EFS = event-free survival; PFR = progression free rate; R/R = relapsed/refractory; MRD = minimal residual disease; CRS = cytokine release syndrome; SCT = stem cell transplant

B-Cell Precursor Acute Lymphoblastic Leukemia

Relapsed or Refractory Disease							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Tisagenlecleucel	2A	Yes (for patients up to 25 years old	Phase 2 (ELIANA), single-cohort, open-label, multicenter	N/A	Overall remission rate within 3 months (CR or CR with incomplete blood count recovery)	R/R B-cell ALL	• A single infusion of tisagenlecleucel provided an overall remission rate of 81% at 3 months with long-term persistence in pediatric and young adult patients with relapsed or refractory B-cell ALL, with transient high-grade toxic effects.
Blinatumomab	1 for relapsed/ refractory Philadelphia-chromosome negative B-ALL	Yes (18 years or older)	Phase 3 (TOWER), randomized	Standard of care: • FLAG ± anthracycline-based regimen • HiDAC-based regimen	OS	Relapsed or refractory disease	• Treatment with blinatumomab resulted in significantly longer OS than chemotherapy

				• High-dose methotrexate-based regimen • Clofarabine-based regimen			
Inotuzumab ozogamicin	1 for relapsed/ refractory Philadelphia-chromosome negative B-ALL	Yes (18 years or older)	Phase 3 (INO-VATE), randomized, open-label	Standard of care: • FLAG • HiDAC-based regimen	CR and OS	Relapsed or refractory CD22-positive Ph+ or Ph-negative ALL in patients due for first or second salvage treatment. Ph+ patients were required to have failed treatment with at least 1 TKI and standard chemotherapy	• Patients receiving inotuzumab ozogamicin versus standard care achieved higher response, MRD-negativity rates, and prolonged PFS and OS

B-Cell Lymphomas

Large B-Cell Lymphoma (use in Richter's transformation is not recommended by NCCN)							
Regimen	**NCCN Category**	**FDA Approved**	**Trial Design**	**Comparator**	**Primary End-Point**	**Line of Therapy**	**Conclusion**
Tisagenlecleucel	2A	Yes (DLBCL not otherwise specified [NOS], high	Phase 2 (JULIET), single-arm, open-label, multicenter	N/A	ORR	R/R DLBCL (after ≥ 2 lines of chemo, including rituximab and anthracycline, and were ineligible for or had	• In relapsed or refractory diffuse large B-cell lymphoma in adults, high rates of durable responses were produced with the use of

		grade B-cell lymphoma, DLBCL arising from follicular lymphoma [FL])				relapsed following auto-HSCT)	tisagenlecleucel (ORR 52% and 12-mon estimated relapse-free survival of 65%).
Axicabtagene ciloleucel	2A	Yes (DLBCL NOS, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, DLBCL arising from follicular lymphoma [FL])	Phase 2 (ZUMA-1), multicenter	N/A	ORR	Refractory disease	• Patients with refractory large B-cell lymphoma who received CAR T-cell therapy with axi-cel had an ORR of 82%, with a safety profile that included myelosuppression, the cytokine release syndrome, and neurologic events.