



Kymriah (tisagenlecleucel)

Last Review Date: January 1, 2019

Number: MG.MM.PH.41dv2

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Definitions

Kymriah (tisagenlecleucel) is a CD19-directed genetically modified autologous T cell immunotherapy indicated 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 and adult patients with relapsed or refractory 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.

Kymriah (tisagenlecleucel) is comprised of autologous T cell that are genetically modified using a lentiviral vector to encode an anti-CD19 chimeric antigen receptor (CAR). The CAR is comprised of a murine single-chain antibody fragment (scFv) specific for CD19, followed by a CD8 hinge and transmembrane region that is fused to the intracellular signaling domains for 4-1BB (CD137) and CD3 zeta.

Kymriah (tisagenlecleucel) is prepared from the patient's own peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. These cells are then enriched for T cells, transduced with the lentiviral vector, and activated with anti-CD3/CD28 antibody coated beads.

Kymriah (tisagenlecleucel) is provided in a single patient-specific infusion bag which may contain up to 2.5×10^8 CAR-positive T cells and is dosed according to indication and patient weight reported at time of leukapheresis:

- Pediatric and young adult B-cell ALL
 - Patients ≤ 50 kg: 0.2 to 5.0×10^6 CAR-positive T cells per kg of body weight
 - Patients > 50 kg: 0.1 to 2.5×10^8 CAR-positive viable T cells

- Adult relapsed or refractory diffuse large B-cell lymphoma
 - 0.6 to 6.0 x 10⁸ CAR-positive viable T cells

Guideline

Provider must submit documentation (which may include office notes and lab results) supporting that the patient has met all approval criteria.

Kymriah (tisagenlecleucel) may be considered medically necessary for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) when all the below criteria are met:

- The patient is between 3 and 25 years of age; **AND**
- The patient has a confirmed diagnosis of B-cell precursor acute lymphoblastic leukemia (ALL); **AND**
- The patient has confirmed CD 19-positive disease; **AND**
- The 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 allogenic stem cell transplantation (SCT); **OR**
 - The patient has been treated with 2 cycles of standard chemotherapy and has not achieved complete response; **OR**
 - The patient experienced a relapse, was treated with 1 cycle of standard chemotherapy and has not achieved complete response; **OR**
 - If the patient has Philadelphia chromosome (Ph)-positive disease has a contraindication to, is intolerant to, or has failed two lines of tyrosine kinase inhibitor (TKI) therapy; **AND**
- The patient has a life expectancy > 12 weeks; **AND**
- The patient has a performance status (Karnofsky or Lansky) ≥ 50%; **AND**
- The patient is not currently pregnant; **AND**
- If the patient is a sexually- active female of reproductive potential has had pregnancy status verified through a pregnancy test; **AND**
- The patient does not have a clinically significant active infection or inflammatory disorder; **AND**
- The patient has not received live vaccines within 2 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah (tisagenlecleucel) treatment, and will not receive live vaccines until immune recovery following 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**
- The patient will be using Kymriah (tisagenlecleucel) in conjunction with lymphodepleting chemotherapy (fludarabine 30 mg/m² intravenously daily for 4 days and cyclophosphamide 500 mg/m² intravenously for 2 days starting with the first dose of fludarabine); **AND**
- Kymriah (tisagenlecleucel) will be infused 2 to 14 days after completion of lymphodepleting chemotherapy; **AND**
- The patient will be premedicated with acetaminophen and diphenhydramine (or another H1-antihistamine) 30 to 60 minutes prior to infusion of Kymriah (tisagenlecleucel); **AND**
- Tocilizumab and emergency equipment are available prior to infusion of Kymriah (tisagenlecleucel) and during the recovery period; **AND**

- The requesting provider belongs to a healthcare facility that has enrolled in the Kymriah REMS program and training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities; **AND**
- Kymriah (tisagenlecleucel) infusion will occur at a treatment center that is certified to administer Kymriah (tisagenlecleucel); **AND**
- The patient will be monitored for signs and symptoms of Cytokine Release Syndrome (CRS) for at least 4 weeks after treatment with Kymriah (tisagenlecleucel) and will be counselled to seek immediate medical attention should signs and symptoms of CRS or a neurological event occur at any time; **AND**
- The patient will stay within proximity (within 2 hours) of the Kymriah (tisagenlecleucel) treatment site for at least 4 weeks following infusion

Kymriah (tisagenlecleucel) may be considered medically necessary for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy when all the below criteria are met:

- The patient is 18 years of age or older; **AND**
- The patient has a confirmed diagnosis of relapsed or refractory large B-cell lymphoma, including:
 - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified; **OR**
 - High grade B-cell lymphoma; **OR**
 - DLBCL arising from follicular lymphoma; **AND**
- The patient's disease is relapsed or refractory, as defined as:
 - Having received 2 or more lines of chemotherapy, including rituximab and anthracycline; **OR**
 - Having relapsed following autologous hematopoietic stem cell transplantation (HSCT)
- The patient has confirmed CD 19-positive disease; **AND**
- The patient has an ECOG performance score ≤ 1 ; **AND**
- The patient has a creatinine clearance ≥ 60 ; **AND**
- The patient's alanine aminotransferase ≤ 5 times normal; **AND**
- The patient's cardiac ejection fraction $\geq 45\%$; **AND**
- The patient's absolute lymphocyte concentration is $\geq 300/\mu\text{L}$; **AND**
- The patient is not currently pregnant; **AND**
- If the patient is a sexually- active female of reproductive potential has had pregnancy status verified through a pregnancy test; **AND**
- The patient does not have a clinically significant active infection or inflammatory disorder; **AND**
- The patient has not received live vaccines within 2 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah (tisagenlecleucel) treatment, and will not receive live vaccines until immune recovery following treatment; **AND**
- The 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**
- The patient will be using Kymriah (tisagenlecleucel) in conjunction with one of the following lymphodepleting chemotherapy regimens:
 - Fludarabine (25 mg/m² i.v. daily for 3 days) and cyclophosphamide (250 mg/m² IV daily for 3 days starting with the first dose of fludarabine); **OR**

- Bendamustin 90 mg/m² i.v. daily for 2 days if a patient experienced a previous Grade 4 hemorrhagic cystitis with cyclophosphamide or demonstrates resistance to a previous cyclophosphamide containing regimen; **OR**
- Lymphodepleting chemotherapy will be omitted due to white blood cell (WBC) count less than or equal to 1 x 10⁹/L within 1 week prior to Kymriah (tisagenlecleucel); **AND**
- Kymriah (tisagenlecleucel) will be infused 2 to 11 days after completion of lymphodepleting chemotherapy, or within 1 week if lymphodepleting chemotherapy is to be omitted; **AND**
- The patient will be premedicated with acetaminophen and diphenhydramine (or another H1-antihistamine) 30 to 60 minutes prior to infusion of Kymriah (tisagenlecleucel); **AND**
- Tocilizumab and emergency equipment are available prior to infusion of Kymriah (tisagenlecleucel) and during the recovery period; **AND**
- The requesting provider belongs to a healthcare facility that has enrolled in the Kymriah REMS program and training has been given to providers on the management of cytokine release syndrome (CRS) and neurological toxicities; **AND**
- Kymriah (tisagenlecleucel) infusion will occur at a treatment center that is certified to administer Kymriah (tisagenlecleucel); **AND**
- The patient will be monitored for signs and symptoms of Cytokine Release Syndrome (CRS) for at least 4 weeks after treatment with Kymriah (tisagenlecleucel) and will be counselled to seek immediate medical attention should signs and symptoms of CRS or a neurological event occur at any time; **AND**
- The patient will stay within proximity (within 2 hours) of the Kymriah (tisagenlecleucel) treatment site for at least 4 weeks following infusion

Limitations/Exclusions

- Approval will be granted for 1 single dose of Kymriah (tisagenlecleucel)
- Coverage cannot be renewed; a maximum of 1 dose per lifetime will apply
- Patient must not have previously received CAR-T or other gene therapy
- Patient must not have a diagnosis of Burkitt's lymphoma/leukemia or a concomitant genetic syndrome (e.g., Fanconi anemia, Kostmann syndrome, Shwachman syndrome, or any other known bone marrow failure syndrome)
- Kymriah (tisagenlecleucel) is not indicated for the treatment of patients with a primary central nervous system lymphoma

Revision History

12/21/2018	Added new code Q2042 – effective January 1, 2019 (Q2040 – discontinued)
7/13/2018	Added coverage and clinical criteria for large B-cell lymphoma
5/1/2018	Clarified clinical criteria and expanded to all lines of business
1/31/2019	Added Diagnosis code Z51.12

Applicable Procedure Codes

Q2042	Tisagenlecleucel, up to 250 million CAR-positive viable T cells, including leukapheresis and dose preparation procedures, per infusion
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Applicable ICD-10 Codes

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 site
C83.39	Diffuse large B-cell lymphoma, extanodal and solid organ sites
C91.00	Acute myeloblastic leukemia, not having achieved remission
C91.02	Acute myeloblastic leukemia, in relapse
Z51.12	Encounter for antineoplastic immunotherapy

References

1. Kymriah [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corp., May 2018.
2. Grupp S, Laetsch T, Buechner J, et al. Analysis of a global registration trial of the efficacy and safety of CTL019 in pediatric and young Adults with relapsed/refractory acute lymphoblastic leukemia (ALL). *Blood*. 2016; 128(22):221.
3. Novartis (2018). Risk Evaluation and Mitigation Strategy (REMS): Cytokine Release Syndrome and Neurological Toxicities [PowerPoint slides] Available at: <http://www.kymriah-rems.com/globalassets/kymriah-rems3/kym-1180086-kymriahremslivetrainingprogram.pdf> Accessed April 2018.
4. 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.