MEDICAL MUTUAL®

Drug Policy

Policy:	**201707**	**Initial Effective Date: 10/13/2017** **Annual Review Date: 01/22/2019** **Last Revised Date: 01/22/2019**
Code(s):	**HCPCS Code Q2042** **NDC Codes:** **Ped ALL: 0078-0846-19** **DLBCL: 0078-0958-19** **Related CPT Codes*:** **0537T; 0538T; 0539T; 0540T**	
SUBJECT:	**Kymriah ® (tisagenlecleucel) suspension for IV infusion**	

*CPT Codes related to Chimeric antigen receptor T-cell (CAR-T) therapy are only approvable if Car-T agent, Kymriah, has been prior approved. If there is no prior approval for Kymriah, the related CPT codes listed above will deny as investigational (M9E).

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

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 for treatment in 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. Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma..[1,4] Kymriah is a type of treatment called chimeric antigen receptor T cell (CAR-T) therapy, which uses the patient's own genetically altered T cells to attack cancer cells. It is the first FDA-approved CAR-T cell therapy. FDA approval is based on the results of the phase II ELIANA trial (NCT02435849). The process of producing Kymriah begins with collecting peripheral blood mononuclear cells from the patient via apheresis. These cells are then sent to a laboratory or a pharmaceutical manufacturing facility where they are genetically engineered to produce CARs on their surface. These reengineered T cells, known as CAR-T cells, are able to recognize an antigen on targeted tumor cells. The CAR-T cells are next stimulated to multiple. The expanded population of CAR-T cells is then prepared for return to a treatment facility where they will be intravenously infused back into the patient. Time from apheresis to infusion is variable; the manufacturer aims to eventually reach a 22-day "vein-to-vein" duration. Patients typically receive a conditioning chemotherapy regimen to deplete T lymphocytes prior to their Kymriah infusion.[3]

Kymriah has black boxed warnings for cytokine release syndrome (CRS) and neurological toxicities. Because of the risk of CRS and neurological toxicities, Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS. Healthcare facilities that dispense and administer Kymriah 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 Kymriah infusion, if needed for treatment of CRS. Certified healthcare facilities must ensure that

healthcare providers who prescribe, dispense or administer Kymriah are trained about the management of CRS and neurological toxicities.[1]

POLICY STATEMENT

This policy involves the use of Kymriah. Prior authorization is recommended for medical and pharmacy benefit coverage of Kymriah. Approval is recommended for those who meet the conditions of coverage in the **Criteria, Dosing, Initial/Extended Approval, Duration of Therapy**, and **Labs/Diagnostics** for the diagnosis provided. The requirement that the patient meet the Criteria for coverage of the requested medication applies to the initial authorization only. **Conditions Not Recommended for Approval** are listed following the recommended authorization criteria. Requests for uses not listed in this policy will be reviewed for evidence of efficacy and for medical necessity on a case-by-case basis.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Kymriah as well as the monitoring required for AEs and long-term efficacy, initial approval requires Kymriah be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals for initial therapy are provided for the initial approval duration noted below; if reauthorization is allowed, a response to therapy is required for continuation of therapy unless otherwise noted below.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Kymriah is recommended in those who meet the following criteria:

Food and Drug Administration (FDA)-Approved Indications

1. Acute Lymphoblastic Leukemia

Criteria. *Patient must meet the following criteria (A, B, C, D, E, F, G, H, I, J, K, L, M, N, O, and P):*

A) Patient is 25 years of age or less and is not pregnant or nursing; AND
B) Patient has been diagnosed with B-cell precursor acute lymphoblastic leukemia (ALL) AND patient meets ONE Of the following criteria (i or ii) [documentation required]
   i. Patient has refractory B-cell ALL with CD 19 tumor expression; OR
   ii. Patient has second or later relapsed ALL with CD19 tumor expression.
C) Patient meets ONE of the following criteria (i, ii, iii, or iv):
   i. Patient has not gone into remission following frontline treatment (primary refractory)- NOTE: Primary refractory as defined by not achieving a CR after 2 cycles of a standard chemotherapy regimen or chemorefractory as defined by not achieving a CR after 1 cycle of standard chemotherapy for relapsed leukemia; OR
   ii. Patient had relapse following second or subsequent complete remissions (post-chemotherapy); OR
   iii. Patient had relapse following hematopoietic stem cell transplant (HSCT) and must be $\geq$ 6 month from stem cell transplantation at the time of Kymriah infusion ; OR
   iv. Patient has refractory disease or experienced a second or later relapse and are ineligible or not a candidate for HSCT.
D) Patient meets ONE of the following criteria (i, ii, or iii):
   i. Patient received a regimen containing 2 lines of tyrosine kinase inhibitor therapy (TKI); OR
   ii. Patient received a regimen containing 2 cycles of a standard chemotherapy regimen

iii. If the patient has Philadelphia Chromosome positive (Ph+) ALL, they have tried and failed, is intolerant to, or has a contraindication to at least 2 tyrosine kinase inhibitors (TKI); **AND**

E) Patient has not previously been treated with a CAR-T Therapy or Kymriah; AND
F) Patient does not have history or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement; AND
G) Patient has Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) performance status ≥ 50 [see Table 1]; AND
H) Kymriah is prescribed by and administered by an oncologist who are trained about the management of CRS and neurological toxicities; AND
I) Patient will receive Kymriah from a certified healthcare facility that is enrolled and complies with Kymriah REMS requirements; AND
J) Patient will be treated with one treatment course of fludarabine and cyclophosphamide lymphodepleting chemotherapy prior to infusion of Kymriah- fludarabine (30 mg/m^2 intravenously daily for 4 days) and cyclophosphamide (500 mg/m^2 intravenously daily for 2 days starting with the first dose of fludarabine).; AND
K) Kymriah will be infused 2 to 14 days after completion of lymphodepleting chemotherapy; AND
L) Kymriah infusion will be delayed if a patient has unresolved serious adverse reactions (including pulmonary reactions, cardiac reactions, or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft vs host disease (GVHD), or worsening of leukemia burden following lymphodepleting chemotherapy; AND
M) Patient will be monitored for signs and symptoms of CRS for at least 2-3 days during the first week following treatment with Kymriah and will be counselled to seek immediate medical attention should signs or symptoms of CRS or a neurological event occur at any time; AND
N) Patient will not receive a G-CSF agent within the first 3 weeks after Kymriah infusion or until CRS has resolved; AND
O) Patient will not receive a live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment and until immune recovery following treatment with Kymriah; AND
P) Patient will stay within 2 hours of the location of the Kymriah infusion for at least 4 weeks after treatment.

Dosing in ALL:
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. The dose is:[1]

- For patients 50 kg or less: administer 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg body weight
- For patients above 50 kg: administer 0.1 to 2.5 x 10^8 CAR-positive viable T cells

Initial Approval/ Extended Approval.
A) *Initial Approval: Approve for 90 days for 1 single-dose of Kymriah per lifetime*
B) *Extended Approval: not recommended*

Duration of Therapy in ALL: 1 single-dose of Kymriah.

Labs/Diagnostics. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing of Kymriah. Monitor immunoglobulin levels after treatment with Kymriah and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement standard guidelines.[1]

2. Non-Hodgkin Lymphoma (NHL): Diffuse Large B-cell lymphoma, relapsed or refractory [1,4]

Criteria. *Patient must meet the following criteria (A, B, C, D, E, F, G,H. I, J, K, L, M,N, O, P, and Q):*

A) Patient is 18 years of age or older and is not pregnant; AND
B) Patient must have CD 19 Tumor expression in bone marrow or peripheral blood [documentation required]; AND
C) Patient has been diagnosed with NHL Large B-cell lymphoma AND patient meets ONE Of the following criteria (i, ii, or iii)
   i. Patient has diffuse large B-cell Lymphoma (DLBCL) not otherwise specified; OR
   ii. Patient has high grade B-cell lymphoma; OR
   iii. Patient has DLBCL arising from follicular lymphoma; AND
D) Patient meets ONE of the following criteria (i, ii, iii or iv):
   i. Patient had relapse following second or subsequent complete remissions (post-chemotherapy); OR
   ii. Patient is chemotherapy-refractory to second-line or later lines of therapy; OR
   iii. Patient has received prior chemotherapy for follicular lymphoma and subsequently have chemorefractory disease and received 2 or more lines of chemotherapy after transformation to DLBCL; OR
   iv. Patient has had prior autologous stem cell transplantation (ASCT) that has progressed within a year post stem cell infusion; AND
E) Previous therapy included anthracycline chemotherapy agent and rituximab; AND
F) Patient has not previously been treated with a CAR-T therapy (i.e. Yescarta) or Kymriah; AND
G) Patient does not have history or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement; AND
H) Kymriah is prescribed by and administered by an oncologist who are trained about the management of CRS and neurological toxicities; AND
I) Asymptomatic or minimally symptomatic with Eastern Cooperative Oncology Group (ECOG) performance status 0-1†; AND
J) Patient does not have history of allogeneic stem cell transplantation; AND
K) Patient will receive Kymriah from a certified healthcare facility that is enrolled and complies with Kymriah REMS requirements; AND
L) Patient will be treated with lymphodepleting chemotherapy: 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 Alternate lymphodepleting chemotherapy: bendamustine 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 [NOTE: Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is less than or equal to 1 x 109/L within 1 week prior to Kymriah infusion.]; AND
M) Kymriah infusion will be delayed if a patient has unresolved serious adverse reactions (including pulmonary reactions, cardiac reactions, or hypotension) from preceding chemotherapies, active uncontrolled infection, active graft vs host disease (GVHD), or worsening of leukemia burden following lymphodepleting chemotherapy; AND

N) Patient will be monitored for signs and symptoms of CRS for at least 2-3 times during the first week following treatment with Kymriah and will be counselled to seek immediate medical attention should signs or symptoms of CRS or a neurological event occur at any time; AND
O) Patient will not receive a G-CSF agent within the first 3 weeks after Kymriah infusion or until CRS has resolved; AND
P) Patient will not receive a live virus vaccine for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Kymriah treatment and until immune recovery following treatment with Kymriah; AND
Q) Patient will stay within proximity of the Kymriah infusion center for at least 4 weeks following infusion.

Dosing in Relapsed or Refractory Diffuse Large B-cell Lymphoma :

Administer 0.6 to 6.0 x 108 CAR-positive viable T cells intravenously 2 to 11 days after completion of the lymphodepleting chemotherapy. NOTE: Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is less than or equal to 1 x 109/L within 1 week prior to KYMRIAH infusion.

Dosing of Kymriah is based on the number of chimeric antigen receptor (CAR)-positive viable T cells.

Initial Approval/ Extended Approval.
A) *Initial Approval: Approve for 90 days for 1 single-dose of Kymriah per lifetime*
B) *Extended Approval: not recommended*

Duration of Therapy in Relapsed or Refractory Diffuse Large B-cell Lymphoma: 1 single-dose of Kymriah.

Labs/Diagnostics. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing of Kymriah. Monitor immunoglobulin levels after treatment with Kymriah and manage using infection precautions, antibiotic prophylaxis and immunoglobulin replacement standard guidelines.[1]

CONDITIONS NOT RECOMMENDED FOR APPROVAL

1. **Active infection or inflammatory disorders.** Do not administer Kymriah to patients with active infection or inflammatory disorders (including TB, HBV, HCV, and HIV).[1]
2. **Primary central nervous system lymphoma**. Kymriah is not indicated for the treatment of patients with primary central nervous system lymphoma, detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases
3. **Richters Syndrome (or Richters Transformation).** Kymriah is not indicated for the treatment of patients with DLBCL that transformed from CLL with Richters Syndrome or Richters Transformation.
4. **Other Cancer Indications**. Coverage is not recommended for circumstances not listed in the Authorization Criteria (FDA-approved indications). Criteria will be updated as new published data are available. [1]

Documentation Requirements:

The Company reserves the right to request additional documentation as part of its coverage determination process. The Company may deny reimbursement when it has determined that the services performed were not medically necessary, investigational or experimental, not within the scope of benefits afforded to the member and/or a pattern of billing or other practice has been found to be either inappropriate or excessive. Additional documentation supporting medical necessity for the services provided must be made available upon request to the Company. Documentation requested may include patient records, test results and/or credentials of the provider ordering or performing a service. The Company also reserves the right to modify, revise, change, apply and interpret this policy at its sole discretion, and the exercise of this discretion shall be final and binding.

REFERENCES

1. Kymriah (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2018.
2. "Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-Cell ALL (ELIANA)." *Determine Efficacy and Safety of CTL019 in Pediatric Patients With Relapsed and Refractory B-Cell ALL - Full Text View - ClinicalTrials.gov*, clinicaltrials.gov/ct2/show/NCT02435849.
3. "Kymriah (tisagenlecleucel)." *Hayesinc.com*, www.hayesinc.com/subscribers/displaySubscriberArticle.do?articleUid=pg.tisagenlecleucel.
4. "Determine Efficacy and Safety of CTL019 in Adult DLBCL Patients (JULIET)." Full Text View - ClinicalTrials.gov, clinicaltrials.gov/ct2/show/NCT02445248.
5. The NCCN Acute Lymphoblastic Leukemia Clinical Practice Guidelines in Oncology (Version 1.2018 – March 12, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 21.2019.
6. The NCCN B-Cell Lymphomas Clinical Practice Guidelines in Oncology (Version 4.2018 – May 15, 2018). © 2018 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed on January 21, 2019.

Table 1. Karnofsky/Lansky Scale

Karnofsky Scale (recipient age ≥ 16 years)		Lansky Scale (recipient age <16 years)	
Able to carry on normal activity; no special care is needed		**Able to carry on normal activity; no special care is needed**	
100	Normal, no complaints, no evidence of disease	100	Fully active
90	Able to carry on normal activity	90	Minor restriction in physically strenuous play
80	Normal activity with effort	80	Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed		**Mild to moderate restriction**	
70	Cares for self, unable to carry on normal activity or to do active work	70	Both greater restrictions of, and less time spent in active play
60	Requires occasional assistance but is able to care for most needs	60	Ambulatory up to 50% of time, limited active play with assistance/supervision
50	Requires considerable assistance and frequent medical care	50	Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly		**Moderate to severe restriction**	
40	Disabled, requires special care and assistance	40	Able to initiate quite activities
30	Severely disabled, hospitalization indicated, although death not imminent	30	Needs considerable assistance for quiet activity
20	Very sick, hospitalization necessary	20	Limited to very passive activity initiated by others (e.g., TV)
10	Moribund, fatal process progressing rapidly	10	Completely disabled, not even passive play

†Eastern Cooperative Oncology Group Performance Status:

Grade 0	Fully active, able to carry on all pre-disease performance without restriction.
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
Grade 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.
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
Grade 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
Grade 5	Dead.

MEDICAL MUTUAL®

Drug Policy

FOR MEDICAL BENEFIT COVERAGE REQUESTS:

Prior approval is required for HCPCS Codes Q2042

CPT Codes related to Chimeric antigen receptor T-cell (CAR-T) therapy are only approvable if Car-T agent, Kymriah, has been prior approved. If there is no prior approval for Kymriah, the related CPT codes listed above will deny as investigational (M9E).

0537T - Chimeric antigen receptor T-cell (CAR-T) therapy; harvesting of blood-derived T lymphocytes for development of genetically modified autologous CAR-T cells, per day

0538T - Chimeric antigen receptor T-cell (CAR-T) therapy; preparation of blood-derived T lymphocytes for transportation (eg, cryopreservation, storage)

0539T - Chimeric antigen receptor T-cell (CAR-T) therapy; receipt and preparation of CAR-T cells for administration

0540T - Chimeric antigen receptor T-cell (CAR-T) therapy; CAR-T cell administration, autologous

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HCPCS Code(s):	
Q2042	Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose (effective 1/1/2019)