PROVIDER POLICIES & PROCEDURES

KYMRIAH™ (TISAGENLECLEUCEL)

The primary purpose of this document is to assist providers enrolled in the Connecticut Medical Assistance Program (CMAP) with the information needed to support a medical necessity determination for Kymriah. By clarifying the information needed for prior authorization of services, HUSKY Health hopes to facilitate timely review of requests so that individuals obtain the medically necessary care they need as quickly as possible.

Kymriah is a genetically modified autologous T cell immunotherapy indicated for the treatment of B-cell precursor acute lympohoblastic leukemia (ALL) that is refractory or in second or later relapse.
Each dose of Kymriah 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 patient to kill the cancer cells.

Kymriah has a boxed warning for cytokine release syndrome (CRS) and neurological toxicities. Kymriah is available only through a program under a Risk Evaluation and Mitigation Strategies (REMS). Healthcare facilities that dispense and administer Kymriah must be enrolled and must comply with REMS requirements. Certified healthcare facilities must have on-site, immediate access to tocilizumab to treat CRS, and ensure that a minimum of two doses of tocilizumab are available for each patient for administration within 2 hours after Kymriah infusion as needed.

Serious infections, some life-threatening or fatal, have occurred in patients after Kymriah infusion. Hepatitis B virus reactivation can occur in patients treated with drugs directed against B cells. Screening should be performed for Hepatitis B virus, Hepatitis C virus, and HIV in accordance with established clinical guidelines prior to the collection of cells for manufacturing.

CLINICAL GUIDELINE

Coverage decisions for the use of Kymriah will be made in accordance with the DSS definition of Medical Necessity. The following criteria are guidelines *only*. Coverage decisions are based on an assessment of the individual and their unique clinical needs. If the guidelines conflict with the definition of Medical Necessity, the definition of Medical Necessity shall prevail. The guidelines are as follows:

I. Kymriah will be considered medically necessary based on the FDA approved indication for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) that meet ALL of the following criteria:
   A. The disease is refractory or in second or later relapse defined as ONE of the following:
      1. Second or greater bone marrow (BM) relapse OR
      2. Any BM relapse after allogeneic stem cell transplantation (SCT) OR

3. 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
4. Individuals with Philadelphia chromosome (Ph) positive disease have a contraindication, intolerance, or have failed two prior lines of tyrosine kinase inhibitor (TKI) therapy OR
5. The individual is not eligible for allogeneic SCT

AND

B. The individual has confirmed CD19 tumor expression

AND

C. The individual is $\leq$ 25 years of age

AND

D. The individual has not previously been treated with gene therapy or Kymriah

AND

E. The individual does not have:
   1. Unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity, or hypotension)
   2. Active infection (including Hepatitis B, Hepatitis C, or HIV infection)
   3. An inflammatory disorder
   4. Active graft versus host disease (GVHD)
   5. Worsening leukemia burden, including active central nervous system (CNS) malignancy involvement

AND

F. The individual is not at risk for Hepatitis B or the individual is at risk for Hepatitis B and Hepatitis B has been ruled out or treatment for Hepatitis B has been initiated

AND

G. The individual has been screened for Hepatitis B, Hepatitis C and HIV before collection of cells for manufacturing

AND

H. Prophylaxis for infection has been followed according to local guidelines

AND

I. The individual has not received live vaccines within 2 weeks prior to the start of lymphodepleting chemotherapy and will not receive live vaccines until immune recovery following Kymriah treatment

AND

J. The individual has received or will receive 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)] within two weeks preceding Kymriah infusion

AND

K. The dose does not exceed one of the following:
   1. Weight less than or equal to 50 kg: 0.2 to 5.0 X 10^6 chimeric antigen receptor (CAR) – positive viable T-cells per kg of body weight intravenously
   2. Weight greater than 50 kg: 0.1 to 2.5 X 10^8 CAR-positive viable T-cells intravenously

AND

L. The prescriber agrees to monitor the individual for signs and symptoms of cytokine release syndrome (CRS) and administer tocilizumab if needed

AND

M. The prescriber agrees to monitor the patient for signs and symptoms of neurological toxicities **AND**
N. The healthcare facility 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

II. Kymriah is typically considered investigational and therefore not medically necessary for all other indications. Again, however, if an individual does not meet these criteria, an assessment of the individual's unique clinical needs will also be conducted.

NOTE: EPSDT Special Provision
Early and Periodic Screening, Diagnosis, and Treatment (EPSDT) is a federal Medicaid requirement that requires the Connecticut Medical Assistance Program (CMAP) to cover services, products, or procedures for Medicaid enrollees under 21 years of age where the service or good is medically necessary health care to correct or ameliorate a defect, physical or mental illness, or a condition identified through a screening examination. The applicable definition of medical necessity is set forth in Conn. Gen. Stat. Section 17b-259b (2011) [ref. CMAP Provider Bulletin PB 2011-36].

PROCEDURE
Prior authorization of Kymriah is required. Coverage determinations will be based upon a review of requested and/or submitted case-specific information.

The following information is needed to review requests for Kymriah:
1. Fully completed State of Connecticut, Department of Social Services HUSKY Health Program Kymriah Prior Authorization Request form (to include physician's order and signature);
2. Clinical information supporting the medical necessity of the treatment as outlined above; and
3. Other information as requested.

Requesting Authorization
Requests for the prior authorization of Kymriah must be submitted by the ordering physician and faxed to the number listed on the request form. Questions regarding this form should be directed to the HUSKY Health Program Utilization Management Department at 1.800.440.5071 (select option for medical authorizations).

Initial Authorization
If approved, authorization will be given for 1 dose only.

Reauthorization
Not applicable

EFFECTIVE DATE
This Policy for the prior authorization of Kymriah for individuals covered under the HUSKY Health Program is effective April 1, 2018.

LIMITATIONS
One time dose per lifetime

CODE:

Code	Definition
Q2040	Tisagenlecleucel, up to 250 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per infusion

DEFINITIONS

1. **HUSKY A**: Connecticut children and their parents or a relative caregiver; and pregnant women may qualify for HUSKY A (also known as Medicaid). Income limits apply.
2. **HUSKY B**: Uninsured children under the age of 19 in higher income households may be eligible for HUSKY B (also known as the Children's Health Insurance Program) depending on their family income level. Family cost-sharing may apply.
3. **HUSKY C**: Connecticut residents who are age 65 or older or residents who are ages 18-64 and who are blind, or have another disability, may qualify for Medicaid coverage under HUSKY C (this includes Medicaid for Employees with Disabilities (MED-Connect), if working). Income and asset limits apply.
4. **HUSKY D**: Connecticut residents who are ages 19-64 without dependent children and who: (1) do not qualify for HUSKY A; (2) do not receive Medicare; and (3) are not pregnant, may qualify for HUSKY D (also known as Medicaid for the Lowest-Income populations).
5. **HUSKY Health Program**: The HUSKY A, HUSKY B, HUSKY C, HUSKY D and HUSKY Limited Benefit programs, collectively.
6. **HUSKY Limited Benefit Program or HUSKY, LBP**: Connecticut's implementation of limited health insurance coverage under Medicaid for individuals with tuberculosis or for family planning purposes and such coverage is substantially less than the full Medicaid coverage.
7. **Medically Necessary or Medical Necessity**: (as defined in Connecticut General Statutes § 17b-259b) Those health services required to prevent, identify, diagnose, treat, rehabilitate or ameliorate an individual's medical condition, including mental illness, or its effects, in order to attain or maintain the individual's achievable health and independent functioning provided such services are: (1) Consistent with generally-accepted standards of medical practice that are defined as standards that are based on (A) credible scientific evidence published in peer-reviewed medical literature that is generally recognized by the relevant medical community, (B)recommendations of a physician-specialty society, (C) the views of physicians practicing in relevant clinical areas, and (D) any other relevant factors; (2) clinically appropriate in terms of type, frequency, timing, site, extent and duration and considered effective for the individual's illness, injury or disease; (3) not primarily for the convenience of the individual, the individual's health care provider or other health care providers; (4) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the individual's illness, injury or disease; and (5) based on an assessment of the individual and his or her medical condition.
8. **Prior Authorization**: A process for approving covered services prior to the delivery of the service or initiation of the plan of care based on a determination by CHNCT as to whether the requested service is medically necessary.

ADDITIONAL RESOURCES AND REFERENCES:

Hartmann J, Schüler-Lenz M, Bondanza A, Buchholz CJ. Clinical development of CAR T cells - challenges and opportunities in translating innovative treatment concepts. EMBO Mol Med. 2017 August 1. http://embomolmed.embopress.org/content/early/2017/07/31/emmm.201607485.long. Accessed on December 18, 2017.

Kymriah [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; August 2017.

National Comprehensive Cancer Network. Acute Lymphoblastic leukemia. Version 5.2017 – October 2017. Available at: https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed on December 19, 2017.

Novartis Pharmaceuticals. Determine efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B-cell ALL (ELIANA). NCT 02435849. Updated July 28, 2017. Available at: https://clinicaltrials.gov/ct2/show/NCT02435849?term=ELIANA&rank=1. Accessed on December 19, 2017.

U.S. Food and Drug Administration. Approved Risk Evaluation and Mitigation Strategies (REMS). Updated 08/30/2017. Available at: https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=indvremsdetails.page&rems=368. Accessed on December 20, 2017.

UpToDate. Treatment of relapsed or refractory acute lymphoblastic leukemia in adults. Last updated 11/21/2017.

PUBLICATION HISTORY

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Original publication	March 2018	Approved by CHNCT Medical Policy Review Committee on January 24, 2018. Approved by DSS on March 13, 2018. Approved by CHNCT Clinical Quality Subcommittee on March 20, 2018.