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Section:	Prescription Drugs	**Effective Date:**	January 1, 2024
Subsection:	Antineoplastic Agents	**Original Policy Date:**	September 8, 2017
Subject:	Kymriah	**Page:**	1 of 7

Last Review Date: December 8, 2023

Kymriah

Description

Kymriah (tisagenlecleucel)

Background
Kymriah (tisagenlecleucel) is a genetically-modified autologous T-cell immunotherapy indicated for the treatment of B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Kymriah is also indicated for the treatment of refractory or relapsed diffuse large B-cell lymphoma (DLBCL) and relapsed or refractory follicular lymphoma in adult patients. Kymriah is a customized treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. The patient'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 (1).

Regulatory Status
FDA-approved indications: Kymriah is a CD19-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of (1):

1. Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.
2. 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.
3. Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Limitations of Use for DLBCL: (1)
Kymriah is not indicated for treatment of patients with primary central nervous system lymphoma.

Kymriah has a boxed warning for cytokine release syndrome (CRS) and neurological toxicities. Patients with an active infection or inflammatory disorders should not receive Kymriah and monitoring for neurological events should be done after treatment of Kymriah (1).

Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (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 (Actemra), 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 (1).

Serious infections, including life-threatening or fatal infections, occurred in patients after Kymriah infusion. Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, can occur in patients treated with drugs directed against B cells. Perform screening for HBV, HCV, and HIV in accordance with clinical guidelines before collection of cells for manufacturing (1).

CD19-directed CAR-T cell therapy is supported by the National Comprehensive Cancer Network (NCCN) Guidelines for the treatment of B-cell lymphomas only after two or more chemoimmunotherapy regimens and if not previously given (2).

The safety and efficacy of Kymriah has not been established in patients above 25 years of age with relapsed or refractory (r/r) B-cell acute lymphoblastic leukemia. The safety and efficacy of Kymriah have not been established in pediatric patients with relapsed or refractory DLBCL or relapsed or refractory follicular lymphoma (1).

Related policies
Breyanzi, Tecartus, Yescarta

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Kymriah may be considered **medically necessary** if the conditions indicated below are met.

Kymriah may be considered **investigational** for all other indications.

Prior-Approval Requirements

Diagnoses

Patient must have **ONE** of the following:

1. Relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
    a. 25 years of age or younger
    b. Documentation of CD19 tumor expression in bone marrow or peripheral blood
    c. Lymphoblasts ≥ 5%
    d. Patient must have received a regimen containing **ONE** of the following, as part of their initial therapy for ALL:
        i. 2 lines of tyrosine kinase inhibitor therapy (TKI)
        ii. 2 cycles of a standard chemotherapy regimen
    e. Patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis

AND NONE of the following:

a. Burkitt lymphoma
b. Grade 2 to 4 graft-versus-host disease (GvHD)
c. Concomitant genetic syndrome associated with bone marrow failure with the exception of Down syndrome
d. Received allogenic cellular therapy within 6 weeks prior to Kymriah infusion
e. Active central nervous system acute lymphoblastic leukemia (i.e., white blood cell count ≥5 cells/μL in cerebrospinal fluid with presence of lymphoblasts)

2. Relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma
    a. 18 years of age or older

b. Patient must have received **TWO** or more lines of systemic therapy including:
   i. Anti-CD20 monoclonal antibody for CD20-positive tumor
   ii. Anthracycline-containing chemotherapy regimen
   iii. Transformed follicular lymphoma **ONLY**: prior chemotherapy for follicular lymphoma and subsequently had chemorefractory disease after transformation to diffuse large B-cell lymphoma
c. **NO** active central nervous system malignancy
d. Patient has adequate organ and bone marrow function as determined by the prescriber

3. Relapsed or refractory follicular lymphoma (FL)
   a. 18 years of age or older
   b. Patient must have received **TWO** or more lines of systemic therapy for the treatment of follicular lymphoma
   c. **NO** active central nervous system malignancy
   d. Patient has adequate organ and bone marrow function as determined by the prescriber

AND ALL of the following for **ALL** indications:
1. Absence of active infection (including TB, HBV, HCV, and HIV)
2. Patient is not at risk for HBV infection **OR** patient is at risk for HBV infection and HBV infection has been ruled out or treatment for HBV infection has been initiated
3. Prescriber agrees to monitor the patient for signs and symptoms of cytokine release syndrome (CRS) and administer tocilizumab (Actemra) if needed
4. Prescriber agrees to monitor the patient for signs and symptoms of neurological toxicities
5. Administered in a healthcare facility enrolled in the Kymriah REMS Program
6. **NO** prior therapy with any other gene therapy (e.g., Abecma, Breyanzi, Carvykti, Tecartus, Yescarta)
7. **NO** dual therapy with any other gene therapy (e.g., Abecma, Breyanzi, Carvykti, Tecartus, Yescarta)

Prior – Approval *Renewal* Requirements

None

Policy Guidelines

Pre – PA Allowance

None

Prior - Approval Limits

Quantity One infusion (only one PA approval for one infusion per lifetime)

Rationale

Summary

Kymriah is an autologous T-cell immunotherapy and is intended for B- cell precursor acute lymphoblastic leukemia (ALL) refractory or in second or later relapse. Kymriah may also be used to treat adult relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and relapsed or refractory follicular lymphoma (FL). Kymriah may cause cytokine release syndrome (CRS) and neurological toxicities. Kymriah should not be administered in patients with an active infection or any inflammatory disorders (1).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of the Kymriah while maintaining optimal therapeutic outcomes.

References

1. Kymriah [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp.; May 2022.
2. NCCN Clinical Practice Guidelines in Oncology® B-Cell Lymphomas (Version 5.2023). National Comprehensive Cancer Network, Inc. July 2023. Accessed on September 29, 2023.
3. NCCN Clinical Practice Guidelines in Oncology® Acute Lymphoblastic Leukemia (Version 2.2023). National Comprehensive Cancer Network, Inc. July 2023. Accessed on September 29, 2023.

Policy History

Date	Action
September 2017	Addition to PA
December 2017	Annual editorial review Change in the age requirement from 2 through 25 to 25 yrs. of age and younger

March 2018	Annual editorial review Removal of the word “autologous” from stem cell requirement and patient from the REMS
May 2018	Addition of the diagnosis of refractory or relapsed diffuse large B-cell lymphoma (DLBCL) in patients 18 years of age or older to criteria.
September 2018	Annual review Addition of: lymphoblasts ≥ 5% for ALL; specific prior lines of therapy for DLBCL; no Burkitt lymphoma, grade 2 to 4 GVHD, concomitant genetic syndrome with the exception of Down syndrome, allogenic cellular therapy within 6 weeks prior to Kymriah infusion, active central nervous system malignancy to ALL; no dual therapy with another CD19-directed CAR-T cell therapy treatment or any other gene therapy per SME
June 2019	Annual review
September 2019	Annual review
June 2020	Annual review
December 2020	Annual editorial review
March 2021	Added the requirement: No prior therapy with another CD19-directed CAR-T cell therapy per NCCN Guidelines. Updated the REMS requirement from prescriber and patient must be enrolled to healthcare facility administering the infusion must be enrolled. Revised PA quantity limit from 1 infusion per lifetime to 1 infusion, 3 months duration. Added clarifying statement indicating that only 1 infusion/one PA approval allowed per member’s lifetime
April 2021	Revised no prior therapy and no dual therapy statements to include any other gene therapy
June 2021	Annual review and reference update
September 2021	Annual review and reference update
March 2022	Per FEP: Removal of requirement for both indications that patient has received prior stem cell transplantation. Addition of requirement for ALL indication that patient has adequate organ function with no significant deterioration in organ function expected within 4 weeks after apheresis. Revision of ALL requirement from absence of concomitant genetic syndrome with the exception of Down syndrome, to absence of concomitant genetic syndrome associated with bone marrow failure with the exception of Down syndrome. Revision of ALL requirement from no active central nervous system malignancy, to no active central nervous system ALL. Addition of requirement for DLBCL indications that patient has adequate organ and bone marrow function as determined by the prescriber

June 2022	Annual review and reference update. Addition of Carvykti to gene therapy requirement
July 2022	Addition of indication - relapsed or refractory follicular lymphoma
September 2022	Annual review and reference update
October 2022	Per FEP, removed duration from PA
December 2022	Annual editorial review
March 2023	Annual review and reference update
June 2023	Annual review and reference update
September 2023	Annual review and reference update
December 2023	Annual review and reference update

Keywords

This policy was reviewed by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.