MEDICAL COVERAGE POLICY	
SERVICE:	**Tisagenlecleucel (Kymriah®)**
Policy Number:	**279**
Effective Date:	**1/1/2024**
Last Review:	**10/26/2023**
Next Review:	**10/26/2024**

Important note: *Unless otherwise indicated, medical policies will apply to all lines of business. Medical necessity as defined by this policy does not ensure the benefit is covered. This medical policy does not replace existing federal or state rules and regulations for the applicable service or supply. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan documents. See the member plan specific benefit plan document for a complete description of plan benefits, exclusions, limitations, and conditions of coverage. In the event of a discrepancy, the plan document always supersedes the information in this policy.*

SERVICE: Tisagenlecleucel (Kymriah®)

PRIOR AUTHORIZATION: Required

POLICY: Please review the plan's EOC (Evidence of Coverage) or Summary Plan Description (SPD) for details.

For Medicare plans, please refer to Medicare NCD 110.24 Chimeric Antigen Receptor (CAR) T-cell Therapy

For Medicaid plans, please confirm coverage as outlined in the Texas Medicaid Provider Procedures Manual | TMHP (TMPPM). Texas Mandate HB154 is applicable for Medicaid plans.

BSWHP may consider tisagenlecleucel (Kymriah®) medically necessary for the treatment of B-cell acute lymphoblastic leukemia (B-ALL) when ALL of the following criteria are met:

1. Member is ≤ 25 years old; **AND**
2. Member diagnosed by a hematologist or oncologist; **AND**
3. CD19 tumor expression is documented; **AND**
4. One-time, single administration treatment**; AND**
5. The member will be receiving treatment at a certified treatment center; **AND**
6. Member has a performance score on Karnofsky or Lansky Scale of ≥ 50% or Eastern Cooperative Oncology Group (ECOG) performance score is 0-3; **AND**
7. Member has relapsed/refractory B-ALL as defined by ONE of the following:
   a. Second or greater bone marrow (BM) relapse
   b. Any BM relapse after allogeneic stem cell transplantation (SCT)
   c. 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)
   d. Patients with Philadelphia chromosome (Ph)-positive disease have contraindication, intolerance, or have failed two prior lines of tyrosine kinase inhibitor (TKI) therapy (e.g., imatinib, dasatinib, ponatinib, etc.)

   AND
8. The member has or will receive lymphodepleting chemotherapy followed by infusion of tisagenlecleucel; **AND**

9. The member will NOT be treated with more than 2.5 x 10^8 viable CAR-T cells AND If the member is less than or equal to 50kg, they will receive weight-based dosing at 0.2-0.5 x 10^6 viable CAR-T cells per kg of body weight; **AND**
10. Member does NOT have any of the following conditions:
    e. Active hepatitis B (HBs AG-positive) or active hepatitis C
    f. Grade 2-4 graft versus host disease
    g. Active central nervous system (CNS) malignancy involvement (i.e. white blood cell (WBC) count greater than or equal to 5 cells/mcl in the cerebral spinal fluid (CSF) with presence of lymphoblasts
    h. On immunosuppression for autoimmune disorder/transplant

    AND
11. Member has NOT previously been treated with CD-19 targeted therapy or prior CD-19 targeted CAR-T cell therapy; **AND**
12. Member has been assessed by a hematologist/oncologist to be an appropriate candidate for apheresis.

Tisagenlecleucel may be considered medically necessary in individuals with large B-cell lymphoma when all of the following criteria are met:

1. Member is 18 years of age or older**; AND**
2. Member diagnosed by a hematologist or oncologist; **AND**
3. Member has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1**; AND**
4. One-time, single administration treatment**; AND**
5. The member will be receiving treatment at a certified treatment center**; AND**
6. The member has relapsed or refractory disease large B-cell lymphoma defined as one of the following:
    a. Large B-cell lymphoma including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma with one of the following:
        i. Progression after two or more lines of systemic therapy (which may or may not include therapy supported by autologous stem cell transplant)**; AND**
        ii. Member must have received adequate prior therapy including at least one of the following:
            - An anthracycline-containing chemotherapy regimen and rituximab; or
            - Either failed autologous hematopoietic stem cell transplantation (ASCT), were ineligible for or refused consent to ASCT
    b. Follicular lymphoma (FL) with one of the following:
        i. Refractory to or relapsed within 6 months after completion of two or more lines of systemic therapy (including an anti-CD20 antibody and an alkylating agent),
        ii. Relapsed during or within six months after completion of an anti-CD20 antibody maintenance therapy following at least two lines of therapy

    AND

7. The member has or will receive lymphodepleting chemotherapy followed by infusion of tisagenlecleucel OR white blood cell count is less than or equal to 1 x 10^9/L within 1 week of tisagenlecleucel administration; **AND**
8. The member will NOT be treated with more than 6 x 10^8 viable CAR-T cells; **AND**
9. Member does NOT have any of the following conditions:
   a. Active hepatitis B (HBs AG-positive) or active hepatitis C
   b. Grade 2-4 graft versus host disease
   c. Active central nervous system (CNS) malignancy involvement (i.e. white blood cell (WBC) count greater than or equal to 5 cells/mcl in the cerebral spinal fluid (CSF) with presence of lymphoblasts
   d. On immunosuppression for autoimmune disorder/transplant

   AND
10. Member has NOT previously been treated with CD-19 targeted therapy or prior CD-19 targeted CAR-T cell therapy; **AND**
11. Member has been assessed by a hematologist/oncologist to be an appropriate candidate for apheresis.

BSWHP considers repeat administration of tisagenlecleucel experimental and investigational because the effectiveness of this strategy has not been established.

BSWHP considers tisagenlecleucel to be experimental and investigational for all other indications.

All requests will be reviewed by a clinical pharmacist and medical director.

BACKGROUND:

Chimeric antigen receptor (CAR) T cells and genetically engineered T-cell receptor (TCR T) cells are manufactured by collecting lymphocytes from a patient or donor and modifying them using gene transfer techniques. Viral vectors are introduced that express cell receptors that are highly specific for tumor antigens. CAR T and TCR T cells are then infused back into the patient, where they direct a targeted immune response to cancerous tissue. CAR T cells express a hybrid receptor with an extracellular single-chain antibody fragment, a transmembrane domain, and at least 1 intracellular signaling domain. CAR T cells are most often used to treat hematological malignancies, and a common target is B-cell cluster of differentiation antigen 19 (CD19)

The U. S. Food and Drug Administration (FDA) approved the Biologics License Application (BLA) for tisagenlecleucel (Kymriah®) (Novartis Pharmaceuticals Corp.) on August 30, 2017 for the treatment of patients up to 25 years of age with B-Cell precursor acute lymphoblastic leukemia (B-ALL) that is refractory or in second or later relapse. The boxed warning includes the clarification that Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) because of the risk of cytokine release syndrome (CRS) and neurological toxicities. See the official drug insert for details.

In a pivotal phase 2 study published by Maude et al, a single infusion of tisagenlecleucel provided durable remission with long-term persistence in pediatric and young adult patients with relapsed or

refractory B-cell ALL, with transient high-grade toxic effects. The overall remission rate within 3 months was 81%, with all patients who had a response to treatment found to be negative for minimal residual disease. It should be noted that CRS occurred in 77% of patients and neurologic events occurred in 40% of patients managed with supportive care.

A study from Memorial Sloan Kettering Cancer Center looked at long-term data in adults with relapsed/refractory B-cell ALL. There were 53 adults in the cohort. The median follow-up was 29 months (range: 1-65), the median event-free survival among the 53 treated patients was 6.1 months and the median overall survival was 12.9 months. Complete remission was observed in 83% of patients.

In a 2016 comprehensive review, Holtzinger et al. (2016) list over 100 ongoing clinical trials evaluating CAR T cells with a variety of targets for a variety of indications. Most of the trials are underway in the United States or Canada, and about a quarter of the trials are underway in China. They also allude to 7 completed phase I trials on CAR T cells for hematological malignancy. The authors conclude that more research is needed to identify ideal CAR T cell targets, receptor designs, and lymphodepletion regimens; control toxic effects like CRS; and evaluate the use of CAR T cells with HSCT.

National Comprehensive Cancer Network (NCCN) gives tisagenlecleucel, for relapsed or refractory B-ALL for patients ≤ 25 years with refractory disease or ≥ 2 relapses and failure of 2 tyrosine kinase inhibitors (TKIs), a recommendation category of 2A.

CODES:

Important note: *Due to the wide range of applicable diagnosis codes and potential changes to codes, an inclusive list may not be presented, but the following codes may apply. Inclusion of a code in this section does not guarantee that it will be reimbursed, and patient must meet the criteria set forth in the policy language.*

CPT Codes:	36511 Therapeutic apheresis; for white blood cells
HCPCS Codes:	Q2042 - Kymriah (Tisagenlecleucel) S2107 Adoptive immunotherapy i.e., development of specific antitumor reactivity (e.g., tumor-infiltrating lymphocyte therapy) per course of treatment
ICD10 codes:	C83.30 - C83.39 Diffuse large B-cell lymphoma C85.20 - C85.29 Primary mediastinal large B-cell lymphoma C91.00 - C91.02 Acute lymphoblastic leukemia D47.Z1 Post-transplant lymphoproliferative disorder
ICD10 Not covered:	

POLICY HISTORY:

Status	Date	Action
New	10/22/2020	New policy
Update	11/19/2020	Added criteria for prescriber, dosing and administration
Update	04/22/2021	Medicaid instructions added.

Update	05/27/2021	Removed Oncology Analytics line, added apheresis criteria, reformatted criteria
Update	07/22/2021	Added clinician reviewer criteria
Update	06/23/2022	Added NCD information
Updated	10/27/2022	Removed language with CMS LCD since NCD applies. Removed Texas Mandate HB1584 language from main policy section as the policy is compliant. Minor formatting update.
Updated	12/01/2022	Added additional follicular lymphoma criteria
Reviewed	10/26/2023	Applied new layout and format.

REFERENCES:

The following scientific references were utilized in the formulation of this medical policy. BSWHP will continue to review clinical evidence related to this policy and make modifications based upon the evolution of the published clinical evidence. Should additional scientific studies become available, and they are not included in the list, please forward the reference(s) to BSWHP so the information can be reviewed by the Medical Coverage Policy Committee (MCPC) and the Quality Improvement Committee (QIC) to determine if a modification of the policy is in order.

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***Note**:*
Health Maintenance Organization (HMO) products are offered through Scott and White Health Plan dba Baylor Scott & White Health Plan, and Scott & White Care Plans dba Baylor Scott & White Care Plan. Insured PPO and EPO products are offered through Baylor Scott & White Insurance Company. Scott and White Health Plan dba Baylor Scott & White Health Plan serves as a third-party administrator for self-funded employer-sponsored plans. Baylor Scott & White Care Plan and Baylor Scott & White Insurance Company are wholly owned subsidiaries of Scott and White Health Plan. These companies are referred to collectively in this document as Baylor Scott & White Health Plan.

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RightCare STAR Medicaid plans are offered through Scott and White Health Plan in the Central Managed Care Service Area (MRSA) and STAR and CHIP plans are offered through SHA LLC dba FirstCare Health Plans (FirstCare) in the Lubbock and West MRSAs.