Clinical Policy: Tisagenlecleucel (Kymriah)

Reference Number: ERX.SPA.220
Effective Date: 12.01.17
Last Review Date: 02.21
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Tisagenlecleucel (Kymriah™) is a CD19-directed genetically modified autologous T-cell immunotherapy.

FDA Approved Indication(s)

Kymriah is 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.
- Adult patients with relapsed or refractory large B-cell lymphoma (LBCL) 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.

Limitation(s) of use: Kymriah is not indicated for treatment of patients with primary central nervous system (CNS) lymphoma.*

**Efficacy of Kymriah for the treatment of LBCL has not been established in patients with a history of or current active, primary, or secondary CNS disease (see Appendix D).*

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Kymriah is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Acute Lymphoblastic Leukemia* (must meet all)**:**

**Only for initial treatment dose; subsequent doses will not be covered.*

1. Diagnosis of B-cell precursor ALL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≤ 25 years;
4. Documentation of CD19 tumor expression;
5. Recent (within the last 30 days) documentation of one of the following (a or b):
   a. Absolute lymphocyte count (ALC) ≥ 500/µL;
   b. CD3 (T-cells) cell count of ≥ 150/µL if ALC < 500/µL;
6. Request meets one of the following (a, b, or c):
   a. Disease is refractory* or member has had ≥ 2 relapses;
      **Refractory is defined as failure to achieve a complete response following induction therapy with ≥ 2 cycles of standard chemotherapy regimen (primary refractory) or after 1 cycle of standard chemotherapy for relapsed leukemia (chemorefractory)*
   b. Disease is Philadelphia chromosome positive: Failure of 2 lines of chemotherapy that included 2 tyrosine kinase inhibitors (e.g., imatinib, Sprycel®, Tasigna®, Bosulif®, Iclusig®) at up to maximally indicated doses, unless clinically significant adverse effects are experienced or all are contraindicated;
      **Prior authorization may be required for tyrosine kinase inhibitors*

c. Member has relapsed following hematopoietic stem cell transplantation (HSCT) and must be ≥ 6 months from HSCT at the time of Kymriah infusion;

7. Dose does not exceed (a or b):
   a. Weight ≤ 50 kg: 5.0 x 10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg of body weight;
   b. Weight > 50 kg: 2.5 x 10^8 CAR-positive viable T cells.

Approval duration: 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) if requested at up to 800 mg per dose)*

B. Large B-Cell Lymphoma* (must meet all)**:**
**Only for initial treatment dose; subsequent doses will not be covered.*

1. Diagnosis of one of the following LBCL (a–f);
   a. DLBCL;
   b. Primary mediastinal large B cell lymphoma (PMBCL);
   c. Transformed follicular lymphoma (TFL) to DLBCL;
   d. Transformed nodal marginal zone lymphoma (MZL) to DLBCL;
   e. High-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma) or high-grade B-cell lymphomas, not otherwise specified;
   f. Monomorphic post-transplant lymphoproliferative disorders (B-cell type);
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Recent (within the last 30 days) ALC ≥ 300/μL;
5. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes Rituxan® and one anthracycline-containing regimen (e.g., doxorubicin);
   **Prior authorization may be required for Rituxan*
6. Member does not have active or primary CNS disease;
7. Dose does not exceed 6.0 x 10^8 CAR-positive viable T cells.

Approval duration: 3 months *(1 dose only, with 4 doses of tocilizumab (Actemra) if requested at up to 800 mg per dose)*

C. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. All Indications in Section I

1. Continued therapy will not be authorized as Kymriah is indicated to be dosed one time only.

Approval duration: Not applicable

B. Other diagnoses/indications

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents;

B. LBCL: Active or primary CNS disease.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALC: absolute lymphocyte count
ALL: acute lymphoblastic leukemia
CAR: chimeric antigen receptor
CML: chronic myelogenous leukemia
CNS: central nervous system
DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration
HSCT: hematopoietic stem cell transplantation
LBCL: large B-cell lymphoma
Ph+: Philadelphia chromosome positive

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Acute Lymphoblastic Leukemia		
imatinib mesylate (Gleevec®)	Adults with Ph+ ALL: 600 mg/day PO Pediatrics with Ph+ ALL: 340 mg/m^2/day PO	Adults: 800 mg/day Pediatrics: 600 mg/day
Sprycel (dasatinib)	Ph+ ALL: 140 mg PO QD	180 mg per day
Iclusig (ponatinib)	Ph+ ALL: 45 mg PO QD	45 mg per day
Tasigna (nilotinib)	Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg PO BID	800 mg/day
Bosulif (bosutinib)	Ph+ CML: 500 mg PO QD	600 mg per day
Various combination regimens that may include the following: daunorubicin, doxorubicin, vincristine, dexamethasone, prednisone, pegaspargase, nelarabine, methotrexate, cyclophosphamide, cytarabine, rituximab, 6-mercaptopurine	Ph- ALL: varies	Varies
Large B-Cell Lymphoma		
First-Line Treatment Regimens		
RCHOP (Rituxan (rituximab), cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (Rituxan (rituximab), cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCDOP (Rituxan (rituximab), cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	Varies	Varies
DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicine) + Rituxan (rituximab)	Varies	Varies
RCEOP (Rituxan (rituximab), cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies
RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone)	Varies	Varies
Second-Line Treatment Regimens		
Bendeka® (bendamustine) ± Rituxan (rituximab)	Varies	Varies
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± Rituxan (rituximab)	Varies	Varies
CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± Rituxan (rituximab)	Varies	Varies
DA-EPOCH ± Rituxan (rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
GDP (gemcitabine, dexamethasone, cisplatin) ± Rituxan (rituximab)	Varies	Varies
gemcitabine, dexamethasone, carboplatin ± Rituxan (rituximab)	Varies	Varies
GemOx (gemcitabine, oxaliplatin) ± Rituxan (rituximab)	Varies	Varies
gemcitabine, vinorelbine ± Rituxan (rituximab)	Varies	Varies
lenalidomide ± Rituxan (rituximab)	Varies	Varies
Rituxan (rituximab)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine) ± Rituxan (rituximab)	Varies	Varies
DHAX (dexamethasone, cytarabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± Rituxan (rituximab)	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide) ± Rituxan (rituximab)	Varies	Varies
MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± Rituxan (rituximab)	Varies	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): none reported
- Boxed warning(s): cytokine release syndrome (CRS), neurological toxicities

Appendix D: General Information

- Refractory ALL is defined as complete remission not achieved after 2 cycles of standard chemotherapy or 1 cycle of standard chemotherapy due to relapsed leukemia.[2]
- CRS, including fatal or life-threatening reactions, occurred in patients receiving Kymriah. Do not administer Kymriah to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab.
- Neurological toxicities, which may be severe or life-threatening, can occur following treatment with Kymriah, including concurrently with CRS. Monitor for neurological events after treatment with Kymriah. Provide supportive care as needed.
- Kymriah is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Kymriah REMS.
- Novartis, the manufacturer of Kymriah, recommends that patients with ALL have an ALC ≥ 500/µL for leukapheresis collection. Patients with an ALC < 500/µL during leukapheresis screening should have had a CD3 (T-cells) cell count of ≥ 150/µL to be eligible for leukapheresis collection.
- The JULIET trial in patients with DLBCL excluded patients with an ALC <300/µL.
- Patients with active CNS disease were excluded in the B2202 trial for ALL and the JULIET trial for DLBCL. NCCN treatment guidelines for ALL state that CNS-directed therapy may include cranial irradiation, itrathecal chemotherapy (e.g., methotrexate, cytarabine, corticosteroids), and/or systemic chemotherapy (e.g., high-dose methotrexate, intermediate or high-dose cytarabine, pegaspargase). For primary DLBCL of the CNS (i.e., primary CNS lymphoma), NCCN treatment guidelines for CNS cancers recommend a high-dose methotrexate induction based

regimen or whole brain radiation therapy, with consolidation therapy with high-dose chemotherapy with stem cell rescue, high-dose cytarabine with or without etoposide, low dose whole brain radiation therapy, or continuation with monthly high-dose methotrexate-based regimen.

- NCCN Pediatric ALL Version 2.2021 treatment guidelines state that Kymriah can be used in relapsed disease that includes medullary and/or extramedullary disease as CAR-T cells have shown activity against extramedullary disease. NCCN defines extramedullary as disease involving the CNS or testes.
- Frigault et al. 2019 reported on their institutional experience with 8 secondary CNS lymphoma patients treated with Kymriah. The best response assessed 28 days post-Kymriah infusion in these patients included complete responses (n = 2) and partial response (n = 2). Additionally, two patients died within 30 days of Kymriah infusion, the remaining two patients experienced disease progression. All patients were receiving CNS-directed therapy for refractory disease up until lymphodepletion.
- Enrollment in the JULIET trial in patients with DLBCL did not require CD19 positive tumor expression. In a subgroup analysis the best overall response rate was comparable between patients with unequivocal CD19 expression (49%, 95% CI 34 to 64, n = 49) and patients with low or negative CD19 expression (50%, 95% CI 29 to 71, n = 24).

V. Dosage and Administration

Indication	Dosing Regimen*	Maximum Dose
ALL	50 kg or less: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight IV Above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells IV	50 kg or less: 5.0 x 10^6 CAR-positive viable T cells per kg of body weight Above 50 kg: 2.5 x 10^8 CAR-positive viable T cells
LBCL	0.6 to 6.0 x 10^8 CAR-positive viable T cells IV	6.0 x 10^8 CAR-positive viable T-cells

*Kymriah should be administered at a certified healthcare facility

VI. Product Availability

Single-dose unit infusion bag: frozen suspension of genetically modified autologous T cells labeled for the specific recipient

VII. References

1. Kymriah Prescribing Information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; May 2018. Available at: https://www.us.kymriah.com/. Accessed November 2, 2020.
2. Data on File. Novartis Pharmaceuticals Corporation; East Hanover, NJ. November 2020.
3. National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia Version 2.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed November 2, 2020.
4. National Comprehensive Cancer Network. Pediatric Acute Lymphoblastic Leukemia Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed November 2, 2020.
5. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed November 2, 2020.
6. National Comprehensive Cancer Network. B-Cell Lymphomas Version 4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed November 2, 2020.
7. National Comprehensive Cancer Network. Central Nervous System Cancers Version 3.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed November 2, 2020.
8. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood. 2019; 134(11): 860-866.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created.	09.26.17	11.17
Criteria added for new FDA indication: adult r/r DLBCL; references reviewed and updated.	05.29.18	08.18
4Q 2018 annual review: added minimum ALC requirement per manufacturer and clinical trial exclusion criteria; for LBCL, clarified requirement of one anthracycline-containing regimen among the two lines of systemic therapy; added hematologist prescriber option; references reviewed and updated.	07.30.18	11.18
Clarified section III diagnoses for which coverage is not authorized from primary CNS lymphoma to active of primary CNS disease to align with clinical trial exclusion criteria and NCCN recommendations; Appendix D was updated to include information related to CNS disease; added requirement in Section IA and IB to confirm "Member does not have active or primary central nervous system (CNS) disease"; LBCL: removed requirement for CD19 tumor expression; references reviewed and updated.	07.16.19	08.19
4Q 2019 annual review: ALL: per NCCN treatment guidelines and clinical trial inclusion criteria modified previous therapy requirement to require one of the following (a, b, or c): a) Disease is refractory or member has had ≥ 2 relapses; b) Disease is Philadelphia chromosome positive: failure of 2 lines of chemotherapy that included 2 tyrosine kinase inhibitors; c) Member has relapsed following HSCT and must be ≥ 6 months from HSCT at the time of Kymriah infusion; references reviewed and updated.	08.15.19	11.19
1Q 2020 annual review: no significant changes; updated therapeutic alternatives to include regimens for Ph-negative ALL; references reviewed and updated.	10.31.19	02.20
Clarified history of or current secondary CNS disease is an exclusion in addition to active and primary CNS disease.	02.17.20	05.20
1Q 2021 annual review: clarified acceptable types of LBCL diagnoses per FDA indication and NCCN compendium; clarified for LBCL in Section I and III that active or primary CNS disease are excluded; for ALL removed exclusion for active CNS disease per NCCN support for use in extramedullary disease; references reviewed and updated.	11.02.20	02.21
Clarified Actemra authorization may be considered if requested.	03.18.21	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.