Clinical Policy: Tisagenlecleucel (Kymriah)

Reference Number: CP.PHAR.361
Effective Date: 12.01.17
Last Review Date: 02.21
Line of Business: Commercial, HIM, Medicaid

Coding Implications
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 active 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.

All requests reviewed under this policy **require medical director review.**

It is the policy of health plans affiliated with Centene Corporation® 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: 5.0×10^6 chimeric antigen receptor (CAR)-positive viable T cells per kg of body weight;
   b. Weight > 50 kg: 2.5×10^8 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 6.0×10^8 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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

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 policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid 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 for all relevant lines of business 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 Pediatrics with Ph+ ALL: 340 mg/m^2/day	Adults: 800 mg/day Pediatrics: 600 mg/day
Sprycel® (dasatinib)	Ph+ ALL: 140 mg per day	180 mg/day
Iclusig® (ponatinib)	Ph+ ALL: 45 mg per day	45 mg/day
Tasigna® (nilotinib)	Resistant or intolerant Ph+ CML-CP and CML-AP: 400 mg twice per day	800 mg/day
Bosulif® (bosutinib)	Ph+ CML: 500 mg per day	600 mg/day

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 (Rituxan® (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: 0.2 to 5.0 x 10^6 CAR-positive viable T cells per kg of body weight IV > 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells IV	≤ 50 kg: 5.0 x 10^6 CAR-positive viable T cells per kg of body weight > 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. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractor difuse large B-cell lymphoma. N Engl J Med 2019; 380(1): 45-56.
9. Frigault MJ, Dietrich J, Martinez-Lage M, et al. Tisagenlecleucel CAR T-cell therapy in secondary CNS lymphoma. Blood. 2019; 134(11): 860-866.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
Q2040	Tisagenlecleucel, up to 250 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per infusion
Q2042	Tisagenlecleucel, up to 600 million car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

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; policies combined for Commercial and Medicaid lines of business; added HIM-Medical Benefit; references reviewed and updated.	05.29.18	08.18
1Q 2019 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	09.25.18	02.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
lines of systemic therapy; added hematologist prescriber option; references reviewed and updated.		
LBCL: Removed requirement for CD19 tumor expression.	02.19.19	05.19
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"; references reviewed and updated.	07.16.19	08.19
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; replaced HIM-Medical Benefit with HIM line of business; updated therapeutic alternatives to include regimens for Ph-negative ALL; added HCPCS codes; references reviewed and updated.	10.31.19	02.20
Section III clarified for LBCL active or primary CNS disease are excluded; for ALL removed exclusion for primary CNS disease as this does not apply; HCPCS code Q2040 removed.	02.17.20	05.20
1Q 2021 annual review: clarified acceptable types of LBCL diagnoses per FDA indication and NCCN compendium; for ALL removed exclusion for active CNS disease per NCCN support for use in extramedullary disease; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated.	11.02.20	02.21
Clarified Actemra authorization may be considered if requested.	03.18.21	
Added disclaimer under Policy/Criteria "All requests reviewed under this policy **require medical director review.**"	05.04.21	

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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical

practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.