Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review. Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	**Submission Date: 02/01/2020**
Policy Number: PA.CP.PHAR.361	**Effective Date: 01/01/2018** **Revision Date: 01/15/2020**
Policy Name: Tisagenlecleucel (Kymriah)	

Type of Submission – Check all that apply:

- ☐ **New Policy**
- ✓ **Revised Policy***
- ☐ **Annual Review - No Revisions**
- ☐ **Statewide PDL -** *Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.*

***All revisions to the policy must be highlighted using track changes throughout the document.**

Please provide any changes or clarifying information for the policy below:

1Q 2020 annual review: 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"; 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; updated therapeutic alternatives to include regimens for Ph-negative ALL; added HCPCS codes; references reviewed and updated.

Name of Authorized Individual (Please type or print):	**Signature of Authorized Individual:**
Francis G. Grillo, MD	Francis Gregory Grillo M.D

Clinical Policy: Tisagenlecleucel (Kymriah)

Reference Number: PA.CP.PHAR.361
Effective Date: 09.26.17
Last Review Date: 01.20

Revision Log

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 lymphoma.

Policy/Criteria
Provider must submit documentation (which may include office chart notes and lab results) supporting that member has met all approval criteria

It is the policy of health plans affiliated with PA Health & Wellness that Kymriah **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

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

1. Diagnosis of B-cell precursor ALL;
2. Age ≤ 25;
3. Prescribed by or in consultation with an oncologist or hematologist;
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 contraindicated or clinically significant adverse effects are experienced;

**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. Member does not have active or primary CNS disease;
8. 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) at up to 800 mg per dose)*

B. Large B-Cell Lymphoma (must meet all)**:**

1. Diagnosis of LBCL;
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) at up to 800 mg per dose)*

C. Other diagnoses/indications

1. Refer to PA.CP.PMN.53 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Acute Lymphoblastic Leukemia: Not Applicable
Continued therapy will not be authorized as Kymriah is indicated to be dosed one time only.

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Refer to PA.CP.PMN.53 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 – PA.CP.PMN.53 or evidence of coverage documents.

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
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,	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cyclophosphamide, doxorubicine) + Rituxan® (rituximab)		
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
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

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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, which 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.
- 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

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 October 31, 2019.
2. Data on File. Novartis Pharmaceuticals Corporation; East Hanover, NJ.
3. National Comprehensive Cancer Network. Acute Lymphoblastic Leukemia Version 2.2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed October 31, 2019.
4. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed October 31, 2019.
5. National Comprehensive Cancer Network. B-Cell Lymphomas Version 5.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed October 31, 2019.
6. National Comprehensive Cancer Network. Central Nervous System Cancers Version 3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed October 31, 2019.
7. 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.
8. National Comprehensive Cancer Network. Pediatric Acute Lymphoblastic Leukemia Version 1.2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed October 31, 2019.

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
1Q 2019 annual review: added minimum ALC requirement per manufacturer and clinical trial exclusion criteria; added criteria for LBCL; added hematologist prescriber option; references reviewed and updated.	01/19	
2Q 2019: LBCL: Removed requirement for CD19 tumor expression.	04/19	
1Q 2020 annual review: 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"; 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; updated therapeutic alternatives to include regimens for Ph-negative ALL; added HCPCS codes; references reviewed and updated.	01/2020	