Clinical Policy Title:	tisagenlecleucel
Policy Number:	RxA.183
Drug(s) Applied:	Kymriah®
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

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

Tisagenlecleucel should be administered at a certified healthcare facility.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
tisagenlecleucel (Kymriah®)	Acute Lymphoblastic Leukemia	50 kg or less: 0.2 to 5 x 10^6 CAR-positive viable T cells per kg of body weight intravenous Greater than 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells intravenous	50 kg or less: 5.0 x 10^6 CAR-positive viable T cells per kg of body weight Greater than 50 kg: 2.5 x 10^8 CAR-positive viable T cells
	Large B-cell Lymphoma	0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based) intravenous	6.0 x 10^8 CAR-positive viable T cells

Dosage Forms

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

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the provisions of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

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

1. Diagnosis of B-cell precursor ALL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age 25 years of age or younger;
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) of 500/µL or greater;
   b. CD3 (T-cells) cell count of 150/µL or greater if ALC is less than 500/µL;
6. Request meets one of the following (a, b, or c):
   a. Disease is refractory* or member has had more than or equal to 2 relapses;
      **Refractory is defined as failure to achieve a complete response following induction therapy with* more than or equal to *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 two (2) lines of chemotherapy that included two (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 six (6) months or greater since HSCT at the time of Kymriah® infusion;
7. Member does not have active or primary central nervous system (CNS) disease;
8. Dose does not exceed (a or b):
   a. Weight of 50 kg or less: 5.0×10^6 chimeric antigen receptor CAR-positive viable T cells per kg of body weight;
   b. Weight greater than 50 kg: 2.5×10^8 CAR-positive viable T cells.

Approval Duration
Commercial: 3 months (1 dose only)
Medicaid: 3 months (1 dose only)

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

1. Diagnosis of one of the following (a or b):
   a. Diffuse large B-cell lymphoma arising from follicular lymphoma;
   b. Histologic transformation of nodal marginal zone lymphoma to DLBCL;
2. Member has one of the following B cell lymphoma subtype (a, b or c) (off-label);

a. High-grade B-cell lymphomas (including High-grade B-cell lymphomas with translocations of MYC and BCL2 and/or BCL6 (double/triple hit lymphoma));
b. Acquired immunodeficiency syndrome (AIDS)-related B-cell lymphomas;
c. Monomorphic post-transplant lymphoproliferative disorders;

3. Prescribed by or in consultation with an oncologist or hematologist;
4. Age 18 years of age or older;
5. Recent (within the last 30 days) ALC of 300/µL or greater;
6. Disease is refractory or member has relapsed after more than or equal to 2 lines of systemic therapy that includes rituximab and one anthracycline-containing regimen (e.g., doxorubicin);
   **Prior authorization may be required.*
7. Member does not have active or primary CNS disease;
8. Dose does not exceed 6.0 x 10^8 CAR-positive viable T cells.

Approval Duration
Commercial: 3 months (1 dose only)
Medicaid: 3 months (1 dose only)

II. Continued Therapy Approval

A. All Indications in Section I

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

Approval Duration
Not applicable

III. Appendices

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
HSCT: Hematopoietic Stem Cell Transplantation
LBCL: Large B-cell Lymphoma
Ph+: Philadelphia Chromosome Positive
AIDS: Acquired immunodeficiency syndrome

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

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

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
Sprycel® (dasatinib)	140 mg per day	180 mg/day
Iclusig® (ponatinib)	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
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
GDP (gemcitabine, dexamethasone, cisplatin) ± Rituxan® (rituximab)	Varies	Varies
gemcitabine, dexamethasone, carboplatin ± Rituxan® (rituximab)	Varies	Varies
GemOx (gemcitabine, oxaliplatin) ± Rituxan® (rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/Maximum Dose
gemcitabine, vinorelbine ± Rituxan® (rituximab)	Varies	Varies
lenalidomide ± Rituxan® (rituximab)	Varies	Varies
Rituxan® (rituximab)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine) ± 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.
- CRS, including fatal or life-threatening reactions, occurred in patients receiving tisagenlecleucel. Do not administer tisagenlecleucel 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 tisagenlecleucel, including concurrently with CRS. Monitor for neurological events after treatment with tisagenlecleucel. Provide supportive care as needed.
- Tisagenlecleucel is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the tisagenlecleucel REMS.
- Novartis, the manufacturer of tisagenlecleucel, recommends that patients with ALL have an ALC more than or equal to 500/µL for leukapheresis collection. Patients with an ALC less than 500/µL during leukapheresis screening should have had a CD3 (T-cells) cell count of more than or equal to 150/µL to be eligible for leukapheresis collection.
- The JULIET trial in patients with DLBCL excluded patients with an ALC less than 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, intrathecal 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).

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy reviewed 1. Clinical Policy Title was updated. 2. Drug(s) Applied was updated. 3. Line of Business Policy Applies to was update to all lines of business. 4. Initial Approval criteria: Commercial and Medicaid approval duration were updated. 5. References were updated.	07/14/2020	09/14/2020
Policy was reviewed. 1. Initial approval criteria I.B.1 updated to include the indication of "Histologic transformation of nodal marginal zone lymphoma to DLBCL".	03/02/2021	06/10/2021

2. Initial approval criteria I.B.2 was updated to include off label indications. 3. Therapeutic alternative verbiage was updated to “Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements”. 4. References were reviewed and updated		