Clinical Policy: Lisocabtagene Maraleucel (Breyanzi)

Reference Number: CP.PHAR.483
Effective Date: 02.05.21
Last Review Date: 05.23
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
Lisocabtagene maraleucel (Breyanzi®) is a CD19-directed genetically modified autologous T-cell immunotherapy.

FDA Approved Indication(s)
Breyanzi is indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy
- Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age
- Relapsed or refractory disease after two or more lines of systemic therapy

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

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 Breyanzi is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. 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 – h);
   a. DLBCL;
   b. DLBCL transformed from one of the following (i – v):
      i. Follicular lymphoma;
      ii. Nodal marginal zone lymphoma;
      iii. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma;

iv. Nongastric MALT Lymphoma (noncutaneous);
v. Splenic marginal zone lymphoma;
c. Primary mediastinal LBCL;
d. Follicular lymphoma grade 3B;
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);
g. HIV-related DLBCL, primary effusion lymphoma, and HHV8-positive DLBCL;
h. T cell/histiocyte-rich LBCL and request is for second line therapy;

2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Request is for one of the following (a, b, or c):
   a. Disease is refractory or member has relapsed after ≥ 2 lines of systemic therapy that includes an anti-CD20 therapy (e.g., rituximab) and one anthracycline-containing regimen (e.g., doxorubicin);*
   b. Disease that is refractory (defined as no complete remission) to or has relapsed (defined as complete remission followed by biopsy-proven disease relapse) no more than 12 months after first-line chemoimmunotherapy that included an anti-CD20 monoclonal antibody (e.g., rituximab*) and anthracycline-containing regimen (e.g., doxorubicin);
   c. Member is not eligible for HSCT due to comorbidities or age (see *Appendix D* for examples) and disease is refractory (defined as no complete remission) to or has relapsed (defined as complete remission followed by biopsy-proven disease relapse) after first-line chemoimmunotherapy that included an anti-CD20 monoclonal antibody (e.g., rituximab*) and anthracycline-containing regimen (e.g., doxorubicin);
   **Prior authorization may be required for rituximab*
5. Member does not have primary CNS disease;
6. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma®, Carvykti™, Kymriah™, Tecartus™, Yescarta™);
7. Breyanzi is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Kymriah, Tecartus, Yescarta);
8. Dose does not exceed 110 x 10^6 chimeric antigen receptor (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. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Large B-Cell Lymphoma

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

Approval duration: Not applicable

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: 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. Primary CNS disease.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALC: absolute lymphocyte count
CAR: chimeric antigen receptor
CNS: central nervous system
CRS: cytokine release syndrome
DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration

HSCT: hematopoietic stem cell transplantation
LBCL: large B-cell lymphoma
MALT: mucosa-associated lymphoid tissue

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
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, doxorubicin) + Rituxan® (rituximab)	Varies	Varies
RCEOP (Rituxan® (rituximab), cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies
RGCVP (Rituxan®, 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
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± Rituxan® (rituximab)	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
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 and neurologic toxicities

Appendix D: General Information

- Patients with primary CNS disease were excluded from the TRANSCEND NHL 001 trial. For primary CNS lymphoma, NCCN treatment guidelines for CNS cancers recommend a high-dose methotrexate induction based regimen or whole brain radiation therapy, and 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.
- In the TRANSCEND NHL 001 trial, three of six patients in the efficacy-evaluable set with secondary CNS lymphoma achieved a complete response.
- No prespecified threshold for blood counts, including absolute lymphocyte count, was required for enrollment in the TRANSCEND NHL 001 trial.
- The PILOT study evaluated transplant-ineligible patients with relapsed or refractory LBCL after one line of chemoimmunotherapy. The study required at least one of the following criteria to identify patients who were not eligible for high-dose therapy and autologous HSCT: age ≥ 70 years, adjusted diffusing capacity of the lung for carbon monoxide (DLCO) ≤ 60%; left ventricular ejection fraction (LVEF) < 50%; creatinine clearance < 60mL/min; aspartate transaminase (AST) or alanine aminotransferase (ALT) greater than two times the upper limit or normal, or Eastern Cooperative Oncology Group (ECOG) performance status of 2 (capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours).

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
LBCL after two or more lines of therapy	Target dose: 50 to 110 x 10^6 CAR-positive viable T cells	110 x 10^6 CAR-positive viable T cells
LBCL after one line of therapy	Target dose: 90 to 110 x 10^6 CAR-positive viable T cells	110 x 10^6 CAR-positive viable T cells

VI. Product Availability

Single-dose 5 mL vial: frozen suspension of genetically modified autologous T-cells labeled for the specific recipient

VII. References

1. Breyanzi Prescribing Information. Bothell, WA: Juno Therapeutics, Inc.; June 2022. Available at: https://packageinserts.bms.com/pi/pi_breyanzi.pdf. Accessed January 30, 2023.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT02631044, Study Evaluating the Safety and Pharmacokinetics of JCAR017 in B-cell Non-Hodgkin Lymphoma (TRANSCEND-NHL-001); 21 June 2021. Available at: https://clinicaltrials.gov/ct2/show/NCT02631044?term=lisocabtagene&draw=2&rank=4. Accessed January 30, 2023.
3. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020 September 19; 396: 839-852.
4. National Comprehensive Cancer Network. B-cell Lymphomas Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf. Accessed January 30, 2023.
5. National Comprehensive Cancer Network Drug and Biologics Compendium. Available at http://www.nccn.org/professionals/drug_compendium. Accessed January 30, 2023.
6. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03575351, A Study to Compare the Efficacy and Safety of JCAR017 to Standard of Care in Adult Subjects With High-risk, Transplant-eligible Relapsed or Refractory Aggressive B-cell Non-Hodgkin Lymphomas (TRANSFORM); 10, June 2021. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03575351. Accessed January 30, 2023.
7. Kamdar M, Solomon SR, Arnason JE, et al. Lisocabtagene Maraleucel Versus Standard of Care with Salvage Chemotherapy Followed By Autologous Stem Cell Transplantation As Second-Line Treatment in Patients with Relapsed or Refractory Large B-Cell Lymphoma (TRANSFORM): Results from an interim analysis of an open-label, randomized, phase 3 trial. Lancet 2022; 399: 2294-308.
8. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03483103, Lisocabtagene Maraleucel (JCAR017) as Second-Line Therapy (TRANSCEND-PILOT-017006); 25, April 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT03483103. Accessed January 30, 2023.
9. Sehgal AR, Hildebrandt G, Ghosh N, et al. 2020 ASCO Annual Meeting I, Meeting Abstract: Lisocabtagene maraleucel (liso-cel) for treatment of second-line (2L) transplant noneligible (TNE) relapsed/refractory (R/R) aggressive large B-cell non-Hodgkin lymphoma (NHL): Updated results from the PILOT study. Journal of Clinical Oncology. 20, May 2020; 38 (15): 8040.
10. Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. Lancet Oncol. 2022 Aug; 23 (8): 1066-1077.

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
Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-CD 19 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 pre-emptively.	03.31.20	05.20
Drug is now FDA approved – criteria updated per FDA labeling; removed minimum absolute lymphocyte count requirement; updated reference for HIM off-label use to HIM.PA.154 (replaces HIM.PHAR.21); references reviewed and updated; Added disclaimer under Policy/Criteria "All requests reviewed under this policy require medical director review."	02.08.21	05.21
Clarified per NCCN Compendium additional DLBCL transformed diseases; added supported use for AIDS-related primary effusion lymphoma.	05.27.21	08.21
2Q 2022 annual review: per NCCN added additional AIDS-related uses in diffuse large B-cell lymphoma and HHV8-positive diffuse large B-cell lymphoma; updated HCPCS codes; added pre-emptive indication for relapsed/refractory LBCL in the second-line setting; references reviewed and updated.	03.09.22	05.22
RT4: converted pre-emptive criteria to FDA-approved status per updated prescribing information for relapsed/refractory LBCL in the second-line setting.	07.07.22	08.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
Doxorubicin spelling corrected in Appendix B.	10.19.22	11.22
2Q 2023 annual review: no significant changes; modified AIDS-related DLBCL to HIV-related per NCCN Compendium; references reviewed and updated.	01.30.23	05.23

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.