Clinical Policy: Lisocabtagene Maraleucel (Breyanzi)

Reference Number: PA.CP.PHAR.483
Effective Date: 04/2021
Last Review Date: 04/2024

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), highgrade 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
- Relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least 2 prior lines of therapy, including a Bruton tyrosine kinase inhibitor (BTKi) and a B-cell lymphoma 2 inhibitor (BCL-2i).*
- Relapsed or refractory follicular lymphoma (FL) who have received 2 or more prior lines of systemic therapy.*
- Relapsed or refractory mantle cell lymphoma (MCL) who have received at least 2 prior lines of systemic therapy, including a BTKi.

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 PA Health & Wellness® 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 large B-cell lymphoma;
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 diffuse large B-cell lymphoma, primary effusion lymphoma, and HHV8-positive diffuse large B-cell lymphoma;
h. T cell/histiocyte-rich LBCL;

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, c or d):
   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);
   d. Member intends to proceed to transplant and has disease that is relapsed or is refractory > 12 months after first-line therapy and had a partial response following second-line therapy;

   **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) at up to 800 mg per dose)***

B. Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma* (must meet all)**:**
**Only for initial treatment dose; subsequent doses will not be covered.*

1. Diagnosis of relapsed or refractory CLL or SLL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. One of the following (a or b):
   a. Member has measurable disease as evidenced by one of the following assessed within the last 30 days (i, ii, or iii):
      i. Measurable lymph nodes ≥ 1.5 cm in the greatest transverse diameter;
      ii. Hepatomegaly;
      iii. Splenomegaly;
   b. Demonstration of CLL cells in the peripheral blood by flow cytometry;
5. Member has received ≥ 2 prior lines of therapy (*see Appendix B for examples*) that include both of the following (a and b):
   a. One BTKi (e.g., Brukinsa®, Calquence®, Imbruvica®);
   b. One BCL2i (e.g., Venclexta®);
   **Prior authorization may be required.*
6. Member does not have active CNS involvement by malignancy or history or presence of clinically relevant CNS pathology (e.g., epilepsy, generalized seizure disorder, aphasia, stroke with current neurologic sequelae, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, cerebral edema, or psychosis);
7. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Kymriah, Tecartus, Yescarta);
8. Breyanzi is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Kymriah, Tecartus, Yescarta);
9. Dose does not exceed 110 x 10^6 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. Follicular Lymphoma* (must meet all)**:**
**Only for initial treatment dose; subsequent doses will not be covered.*

1. Diagnosis of FL grade 1, 2, or 3a;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Disease is relapsed/refractory after ≥ 2 lines of systemic therapy that includes a combination of an anti-CD20 monoclonal antibody (e.g., rituximab or Gazyva®) and an alkylating agent (e.g., bendamustine, cyclophosphamide, chlorambucil)*;
   **Prior authorization may be required*
5. Member does not have CNS-only involvement by malignancy (secondary CNS involvement is allowed);
6. Member does not have history or presence of clinically relevant CNS pathology (e.g., epilepsy, generalized seizure disorder, aphasia, stroke with current neurologic sequelae, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, cerebral edema, or psychosis);
7. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Kymriah, Tecartus, Yescarta);

8. Breyanzi is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Kymriah, Tecartus, Yescarta);
9. Dose does not exceed 100 x 10^6 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)*

D. Mantle Cell Lymphoma* (must meet all)**:**

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

1. Diagnosis of relapsed or refractory MCL;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member has previously received ≥ 2 prior lines of systemic therapy that included all the following (a, b, and c):
   a. Anti-CD20 monoclonal antibody therapy (e.g., rituximab);
   b. BTKi (e.g., Imbruvica, Calquence, Brukinsa, Jaypirca®);
   c. Alkylating agent (e.g., bendamustine, cyclophosphamide, platinum [carboplatin, cisplatin, or oxaliplatin]);
5. Member does not have CNS-only involvement by malignancy (secondary CNS involvement is allowed);
6. Member does not have history or presence of clinically relevant CNS pathology (e.g., epilepsy, generalized seizure disorder, aphasia, stroke with current neurologic sequelae, severe brain injuries, dementia, Parkinson's disease, cerebellar disease, cerebral edema, or psychosis);
7. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Kymriah, Tecartus, Yescarta);
8. Breyanzi is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Carvykti, Kymriah, Tecartus, Yescarta);
9. Dose does not exceed 100 x 10^6 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)*

E. 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): PA.CP.PMN.53

II. Continued Therapy

A. All Indications in Section I:

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

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53;

B. Primary CNS disease.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALC: absolute lymphocyte count
BTKi: Bruton tyrosine kinase inhibitor
BCL2i: B-cell lymphoma 2 inhibitor
CLL: chronic lymphocytic leukemia
CAR: chimeric antigen receptor
CNS: central nervous system
CRS: cytokine release syndrome
DLBCL: diffuse large B-cell lymphoma
FDA: Food and Drug Administration
FL: follicular lymphoma
HSCT: hematopoietic stem cell transplantation
LBCL: large B-cell lymphoma
MALT: mucosa-associated lymphoid tissue
MCL: mantle cell lymphoma
SLL: small lymphocytic lymphoma

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
LBCL: First-Line Treatment Regimens		
RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
RCEPP (rituximab, cyclophosphamide, etoposide, prednisone, procarbazine)	Varies	Varies
RCDOP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristine, prednisone)	Varies	Varies
DA-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) + rituximab	Varies	Varies
RCEOP (rituximab, cyclophosphamide, etoposide, vincristine, prednisone)	Varies	Varies
RGCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, prednisone)	Varies	Varies
LBCL: Second-Line Treatment Regimens		
Bendeka® (bendamustine) ± rituximab	Varies	Varies
CEPP (cyclophosphamide, etoposide, prednisone, procarbazine) ± rituxima)	Varies	Varies
CEOP (cyclophosphamide, etoposide, vincristine, prednisone) ± rituximab	Varies	Varies
DA-EPOCH ± rituximab	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab	Varies	Varies
gemcitabine, dexamethasone, carboplatin ± rituximab	Varies	Varies
GemOx (gemcitabine, oxaliplatin) ± rituximab	Varies	Varies
gemcitabine, vinorelbine ± rituximab	Varies	Varies
lenalidomide ± rituximab	Varies	Varies
Rituximab (Riabni™, Rituxan®, Ruxience®, Truxima®)	Varies	Varies
DHAP (dexamethasone, cisplatin, cytarabine) ± rituximab	Varies	Varies
DHAX (dexamethasone, cytarabine, oxaliplatin) ± rituximab	Varies	Varies
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab	Varies	Varies
ICE (ifosfamide, carboplatin, etoposide) ± rituximab	Varies	Varies
MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab	Varies	Varies
CLL/SLL: First-Line Therapies		
Calquence (acalabrutinib) ± Gazyva® (obinutuzumab)	Varies	Varies
Venclexta® (venetoclax) + Gazyva (obinutuzumab)	Varies	Varies
Brukinsa (zanubrutinib)	160 mg PO BID or 320 mg PO QD	320 mg/day 640 mg/day when used with a moderate CYP3A4 inducer
Imbruvica® (ibrutinib)	420 mg PO QD	420 mg/day
Imbruvica (ibrutinib) + Gazyva (obinutuzumab)	Varies	Varies
Imbruvica (ibrutinib) + rituximab	Varies	Varies
Imbruvica (ibrutinib) + Venclexta (venetoclax)	Varies	Varies
CLL/SLL: Second-Line or Third-Line Therapies		
Calquence (acalabrutinib)	100 mg PO BID	400 mg/day
Venclexta (venetoclax) ± rituximab	Varies	Varies
Brukinsa (zanubrutinib)	160 mg PO BID or 320 mg PO QD	320 mg/day 640 mg/day when used with a moderate CYP3A4 inducer
Imbruvica (ibrutinib)	420 mg PO QD	420 mg/day

CLL/SLL: Therapies for Relapsed or Refractory Disease After Prior BTKi- and BCL2i-Based Regimens		
Copiktra® (duvelisib)	25 mg PO BID	50 mg/day
Zydelig® (idelalisib) ± rituximab	150 mg PO BID	300 mg/day
Jaypirca™ (pirtobrutinib)	200 mg PO QD	200 mg/day
FCR (fludarabine, cyclophosphamide, rituximab)	Varies	Varies
Revlimid® (lenalidomide) ± rituximab	Varies	Varies
Gazyva (obinutuzumab)	100 mg IV on day 1, 900 mg IV on day 2 of cycle 1, then 1,000 mg IV on days 8 and 15 of cycle 1; begin the next cycle of therapy on day 29. For cycles 2 to 6, give 1,000 mg IV on day 1 repeated every 28 days.	See regimen
Campath® (alemtuzumab) ± rituximab	30 mg/day IV three times per week for 12 weeks	See regimen
CLL/SLL: Therapies for Relapsed or Refractory Disease After Prior BTKi- and BCL2i-Based Regimens		
High-dose methylprednisolone ± rituximab or Gazyva (obinutuzumab)	Varies	Varies
FL First-Line and Second-Line + Subsequent Treatment Regimens		
bendamustine + (Gazyva® (obinutuzumab) or rituximab)	Varies	Varies
CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + (Gazyva® (obinutuzumab) or rituximab)	Varies	Varies
CVP (cyclophosphamide, vincristine, prednisone) + Gazyva® (obinutuzumab) or rituximab	Varies	Varies
rituximab ± (lenalidomide, chlorambucil, or cyclophosphamide)	Varies	Varies
rituximab	Varies	Varies
Gazyva® (obinutuzumab)	Varies	Varies
Zevalin® (ibritumomab tiuxetan)	Varies	Varies
MCL		
HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone/methotrexate/ cytarabine) + rituximab	Varies	Varies
NORDIC (rituximab + cyclophosphamide, vincristine, doxorubicin, prednisone/rituximab + cytarabine)	Varies	Varies

RCHOP/RDHAP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)/(rituximab, dexamethasone, cisplatin, cytarabine)	Varies	Varies
RDHA (rituximab, dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin)	Varies	Varies
RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)	Varies	Varies
Bendeka® (bendamustine) ± rituximab	Varies	Varies
VR-CAP (bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone)	Varies	Varies
Revlimid® (lenalidomide) + rituximab	Varies	Varies
bortezomib ± rituximab	Varies	Varies
lenalidomide ± rituximab	Varies	Varies
Imbruvica® (ibrutinib) ± rituximab	560 mg PO QD	560 mg/day
Calquence® (acalabrutinib)	100 mg PO BID	400 mg/day
MCL		
Brukinsa® (zanubrutinib)	160 mg PO BID or 320 mg PO QD	320 mg/day
Jaypirca® (pirtobrutinib)	200 mg PO QD	200 mg PO QD
Venclexta® (venetoclax)	20 mg/day for week 1, 50 mg/day for week 2, 100 mg/day for week 3, 200 mg/day for week 4, 400 mg/day for week 5. Week 6 and thereafter: 800 mg/day	800 mg/day

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, CLL/SLL, FL, MCL	Target dose: 90 to 110 x 10^6 CAR-positive viable T cells	110 x 106 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

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12. Siddiqi T, Maloney DG, Kenderian SS, et al. Lisocabtagene maraleucel in chronic lymphocytic leukaemia and small lymphocytic lymphoma (TRANSCEND CLL 004): a multicentre, open-label, single-arm, phase 1-2 study. Lancet. 2023 Aug 19;402(10402):641-654.
13. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03331198, Study Evaluating Safety and Efficacy of JCAR017 in Subjects With Relapsed or Refractory Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL); 29, August 2023. Available at: https://clinicaltrials.gov/study/NCT03331198. Accessed March 18, 2024.
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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
Policy created.	04/2021
2Q 2022 annual review: clarified per NCCN Compendium additional DLBCL transformed diseases; added supported use for AIDS-related primary effusion lymphoma;.per NCCN added additional AIDS-related uses in diffuse large B-cell lymphoma and HHV8-positive diffuse large B-cell lymphoma; updated HCPCS codes; references reviewed and updated.	04/2022
RT4: FDA-approved status per updated prescribing information for relapsed/refractory LBsCL in the second-line setting; references reviewed and updated.	10/2022
2Q 2023 annual review: no significant changes; modified AIDS-related DLBCL to HIV-related per NCCN Compendium; references reviewed and updated.	04/2023
2Q 2024 annual review: for T-cell/histiocyte-rich LBCL removed requirement for use as second line therapy; references reviewed and updated.	04/2024
RT4: added new indications for CLL/SLL, FL and MCL.	06/2024