Clinical Policy: Ciltacabtagene Autoleucel (Carvykti)

Reference Number: LA.PHAR.533
Effective Date: 09.29.23
Last Review Date: 10.11.24 ~~03.25.24~~
Line of Business: Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

****Please note: This policy is for medical benefit****

Description
Ciltacabtagene autoleucel (Carvykti™) is a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy.

FDA Approved Indication(s)
Caryvkti is indicated for the treatment of ~~adults~~adult patients with relapsed ~~and/~~or refractory multiple myeloma (MM~~) after four or more~~), who have received at least 1 prior ~~lines~~line of therapy, including a proteasome inhibitor (PI~~),~~) and an immunomodulatory agent (IMiD), and ~~an anti-CD38 monoclonal antibody~~are refractory to lenalidomide.

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.

It is the policy Louisiana Healthcare Connections® that Carvykti is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Multiple Myeloma* (must meet all)**:**

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

1. Diagnosis of relapsed or refractory MM;
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. Serum M-protein ≥ ~~1~~0.5 g/dL;
      ii. Urine M-protein ≥ 200 mg/24 h;
      iii. Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal;
   b. Member has progressive disease, as defined by the IMWG response criteria (see *Appendix D*), assessed within 60 days following the last dose of the last anti-myeloma drug regimen received;

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5. Member has lenalidomide-refractory disease (i.e., disease progression within 60 days of completing lenalidomide therapy, *see Appendix D*);
5.6. Member has received ≥ 4at least one prior ~~lines~~line of therapy (*see Appendix B for examples*~~)~~), that ~~include all~~included both of the following (a~~, b,~~ and ~~c~~b):
   a. A PI (e.g., bortezomib, Kyprolis®, Ninlaro®);
   b. An IMiD (e.g., Revlimid®, Pomalyst®, Thalomid®);
   ~~c. An anti-CD38 antibody (e.g., Darzalex®/Darzalex Faspro™, Sarclisa®);~~
   **Prior authorization may be required. Induction with or without hematopoietic stem cell transplant, consolidation and ~~with or without~~ maintenance therapy is considered a single ~~regimen~~line of therapy.*
6.7. Member does not have active or prior history of central nervous system (CNS) involvement (e.g., seizure, cerebrovascular ischemia) or exhibit clinical signs of meningeal involvement of MM;
7.8. Member has not previously received treatment with anti-BCMA targeted therapy (e.g., Blenrep™, Tecvayli™);
8.9. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma®, Breyanzi®, Kymriah™, Tecartus™, Yescarta™);
9.10. Carvykti is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Kymriah, Tecartus, Yescarta);
10.11. Dose does not exceed 1 x 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. 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 LA.PMN.255
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:~~ LA.PMN.53 for Medicaid.

II. Continued Therapy

A. Multiple Myeloma:
1. Continued therapy will not be authorized as Carvykti 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 LA.PMN.255
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:~~ LA.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 – LA.PMN.53 for Medicaid or evidence of coverage documents;

B. Active or prior history of CNS involvement (e.g., seizure, cerebrovascular ischemia) or exhibit clinical signs of meningeal involvement of MM.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BCMA: B-cell maturation antigen
CAR: chimeric antigen receptor
CNS: central nervous system
CRS: cytokine release syndrome
FDA: Food and Drug Administration
FLC: free light chain
GBS: Guillain-Barré syndrome
ICANS: immune effector cell-associated neurotoxicity syndrome
IMiD: immunomodulatory drug
IMWG: International Myeloma Working Group
MM: multiple myeloma
PI: proteasome inhibitor

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
bortezomib/Revlimid® (lenalidomide)/dexamethasone	Varies	Varies
bortezomib/cyclophosphamide/dexamethasone	Varies	Varies
bortezomib/doxorubicin (or liposomal doxorubicin)/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib) Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib)/cyclophosphamide/ dexamethasone	Varies	Varies
Kyprolis® (carfilzomib – weekly or twice weekly)/ dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/dexamethasone	Varies	Varies
Ninlaro® (ixazomib)/pomalidomide/dexamethasone	Varies	Varies
bortezomib/dexamethasone	Varies	Varies
bortezomib/Thalomid® (thalidomide)/dexamethasone	Varies	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
cyclophosphamide/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Revlimid® (lenalidomide)/dexamethasone	Varies	Varies
VTD-PACE (dexamethasone/Thalomid® (thalidomide)/ cisplatin/doxorubicin/cyclophosphamide/etoposide/ bortezomib)	Varies	Varies
Revlimid® (lenalidomide)/low-dose dexamethasone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/bortezomib/ melphan/prednisone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/ bortezomib/dexamethasone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/Revlimid® (lenalidomide)/dexamethasone	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)	Varies	Varies
Darzalex® (daratumumab) or Darzalex Faspro™ (daratumumab/hyaluronidase-fihj)/pomalidomide/ dexamethasone	Varies	Varies
Empliciti® (elotuzumab)/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
Empliciti® (elotuzumab)/bortezomib/dexamethasone	Varies	Varies
Empliciti® (elotuzumab)/pomalidomide/dexamethasone	Varies	Varies
bendamustine/bortezomib/dexamethasone	Varies	Varies
bendamustine/Revlimid® (lenalidomide)/ dexamethasone	Varies	Varies
panobinostat/bortezomib/dexamethasone	Varies	Varies
panobinostat/Kyprolis® (carfilzomib)	Varies	Varies
panobinostat/Revlimid® (lenalidomide)/dexamethasone	Varies	Varies
pomalidomide/cyclophosphamide/dexamethasone	Varies	Varies
pomalidomide/dexamethasone	Varies	Varies
pomalidomide/bortezomib/dexamethasone	Varies	Varies
pomalidomide/Kyprolis® (carfilzomib)/dexamethasone	Varies	Varies
Sarclisa® (isatuximab-irfc)/pomalidomide/ dexamethasone	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), neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, ~~and~~ prolonged and recurrent cytopenia, secondary hematological malignancies

Appendix D: General Information

- In the CARTITUDE-1 trial, induction with or without hematopoietic stem cell transplant and with or without maintenance therapy was considered a single line of therapy. Patients were required to have undergone at least one complete cycle of treatment for each line of therapy, unless progressive disease was the best response to the regimen.
- In the CARTITUDE-1 trial, a line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.
- The clinical trial protocol for CARTITUDE-1 did not define or provide details on the investigator assessment for determining active CNS disease for possible trial exclusion, this was left to the discretion of the principle investigator to determine patient fitness for trial enrollment. According to the NCCN Guidelines for Central Nervous System Cancers for leptomeningeal metastases, MRI or the brain and spine should be performed for accurate staging. A definitive diagnosis is most commonly made by CSF analysis via lumbar puncture with CSF protein that is typically increased, there may be a pleocytosis or decreased glucose levels, and ultimately positive CSF cytology for tumor cells. Most CNS myeloma patients present with cerebral symptoms, such as headaches and cognitive dysfunction, but a significant proportion also can have either spinal root/cord symptoms (e.g., limb sensory changes, motor loss, and urinary retention) or positive spinal leptomeningeal imaging. Given the frequent multi-focality of disease identified on imaging, it is reasonable to routinely perform whole spine imaging in any patient with suspected CNS myeloma
- Patients receiving Carvykti may experience fatal or life-threatening ICANS following treatment with Carvykti, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. ICANS occurred in 23% (22/97) of patients receiving Carvykti including Grade 3 or 4 events in 3% (3/97) and Grade 5 (fatal) events in 2% (2/97).
- Of the 25 patients in the CARTITUDE-1 study experiencing any neurotoxicity, five male patients had neurologic toxicity with several signs and symptoms of parkinsonism, distinct from ICANS. One patient died of neurologic toxicity with parkinsonism 247 days after administration of Carvykti; two patients with ongoing parkinsonism died of

infectious causes 162 and 119 days after administration of Carvykti; in the remaining 2 patients, symptoms of parkinsonism were ongoing up to 530 days after administration of Carvykti.

- A fatal outcome following Guillain-Barré syndrome (GBS) has occurred in another ongoing study of Carvykti despite treatment with intravenous immunoglobulins. Carvykti prescribing information recommends to monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.
- The IMWG response criteria for multiple myeloma definition of progressive disease requires only one of the following:
  - Increase of 25% from lowest response value in any of the following:
    - Serum M-component (absolute increase must be ≥ 0.5 g/dL), and/or
    - Urine M-component (absolute increase must be ≥ 200 mg/24 h), and/or
  - Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL)
  - Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%)
  - Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD (sum of the products of the maximal perpendicular diameters of measured lesions) of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis;
  - ≥ 50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease
- In CARTITUDE-4, subjects enrolled were required to be refractory to lenalidomide per IMWG consensus guidelines (failure to achieve minimal response or progression on or within 60 days of completing lenalidomide therapy). Progression on or within 60 days of the last dose of lenalidomide given as maintenance will meet this criterion. For subjects with more than 1 prior line of therapy, there was no requirement to be lenalidomide refractory to the most recent line of prior therapy.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
MM	0.5 to 1 x10^6 chimeric CAR-positive viable T cells/kg	1 x10^8 chimeric 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. Carvykti Prescribing Information. Horsham, PA: Janssen Biotech, Inc.; ~~March 2022~~April 2024. Available at: https://www.janssenlabels.com/package-insert/product-

monograph/prescribing-information/CARVYKTI-pi.pdf. Accessed ~~January 30, 2023~~April 22, 2024.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03548207, A Study of JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against B-Cell Maturation Antigen (BCMA) in Participants With Relapsed or Refractory Multiple Myeloma (CARTITUDE-1); ~~28 January~~6, October 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT03548207~~?term=NCT03548207.~~. Accessed January ~~30, 2023~~23, 2024.
3. Madduri D, Berdeja JG, Usmani SZ, et al. CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Relapsed/Refractory Multiple Myeloma; ASH 2020. Oral Presentation 177; December 5-8, 2020. Available at: https://ash.confex.com/ash/2020/webprogram/Paper136307.html. Accessed January ~~30, 2023.~~23, 2024.
4. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021 Jun 24; 398 (10297): 314-324.
5. National Comprehensive Cancer Network. Multiple Myeloma Version 3.~~2023~~2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed ~~January 30, 2023~~April 22, 2024.
6. Chen CI, Masih-Khan E, Jiang H, et al. Central nervous system involvement with multiple myeloma: long term survival can be achieved with radiation, intrathecal chemotherapy, and immunomodulatory agents. British Journal of Haematology. August 2013; 162 (4): 483-488.
7. ClinicalTrials.gov. A Study Comparing JNJ-68284528, a CAR-T Therapy Directed Against B-cell Maturation Antigen (BCMA), Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Participants With Relapsed and Lenalidomide-Refractory Multiple Myeloma (CARTITUDE-4). Available at: https://clinicaltrials.gov/ct2/show/NCT04181827. Accessed April 22, 2024.
8. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma. N Engl J Med. 2023 July 27 ;389(4): 335-347.

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
Q2056	Ciltacabtagene autoleucel, up to 100 million autologous B-cell maturation antigen (BCMA) directed CAR-positive T cells, including leukapheresis and dose preparation procedures, per therapeutic dose

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CLINICAL POLICY
Ciltacabtagene Autoleucel

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Policy created	05.01.23	08.28.23
Annual review: added additional option to currently required measurable disease requirement to allow for progressive disease as defined by IMWG; clarified requirement for diagnosis of *relapsed or refractory* multiple myeloma; removed J9999 HCPCS code; references reviewed and updated.	03.25.24	06.20.24
~~u~~Updated boxed warnings to include secondary hematological malignancies per prescribing information; references reviewed and updated. ~~u~~Updated criteria to reflect expanded indication for use after at least one prior line of therapy.	10.11.24	

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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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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.

CLINICAL POLICY
Ciltacabtagene Autoleucel

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.

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