Clinical Policy: Ciltacabtagene Autoleucel (Carvykti)

Reference Number: ERX.SPA.436
Effective Date: 02.28.22
Last Review Date: 05.22
Line of Business: Commercial, Medicaid

Revision Log

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

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 with relapsed and/or refractory multiple myeloma (MM) after four or more prior lines of therapy, including a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 monoclonal antibody.

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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Caryvkti 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 MM;
2. Prescribed by or in consultation with an oncologist or hematologist;
3. Age ≥ 18 years;
4. Member has measurable disease as evidenced by one of the following assessed within the last 30 days (a, b, or c):
   a. Serum M-protein ≥ 1 g/dL;
   b. Urine M-protein ≥ 200 mg/24 h;
   c. Serum free light chain (FLC) assay: involved FLC level ≥ 10 mg/dL (100 mg/L) provided serum FLC ratio is abnormal;
5. Member has received ≥ 4 prior lines of therapy (*see Appendix B for examples*) that include all of the following (a, b, and c):
   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 and with or without maintenance therapy is considered a single regimen.*
6. 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. Member has not previously received treatment with anti-BCMA targeted therapy (e.g., Blenrep™);
8. Member has not previously received treatment with CAR T-cell immunotherapy (e.g., Abecma®, Breyanzi®, Kymriah™, Tecartus™, Yescarta™);
9. Caryvkti is not prescribed concurrently with other CAR T-cell immunotherapy (e.g., Abecma, Breyanzi, Kymriah, Tecartus, Yescarta);

10. 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
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
A. Multiple Myeloma
1. Continued therapy will not be authorized as Caryvkti is indicated to be dosed one time only.
Approval duration: Not applicable

B. Other diagnoses/indications
1. Refer to ERX.PA.01 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 – ERX.PA.01 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
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 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

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.

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.; February 2022. Available at: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/CARVYKTI-pi.pdf . Accessed March 2, 2022.
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 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT03548207?term=NCT03548207. Accessed February 1, 2022.

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 March 9, 2021.
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 Jul 24;398(10297):314-324.
5. National Comprehensive Cancer Network. Multiple Myeloma Version 5.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed March 21, 2022.
6. National Comprehensive Cancer Network. Central Nervous System Cancers Version 2.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Accessed April 5, 2022.
7. 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.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	03.23.21	05.21
2Q 2022 annual review: drug is now FDA approved - criteria updated per FDA labeling: revised prior therapy requirements to ≥ 4 prior lines of therapy (option for double refractory to IMiD and PI removed), updated maximum dose and black box warnings, Appendix D added additional description of CARTITUDE-1 trial protocol definition for prior lines of therapy; references reviewed and updated.	03.21.22	05.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.