NEW DRUG APPROVAL

Brand Name	Carvykti™
Generic Name	ciltacabtagene autoleucel
Drug Manufacturer	Janssen Biotech, Inc.

New Drug Approval

FDA approval date: February 28, 2022

Review designation: N/A

Type of review: Biological License Application (BLA): 125746

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Multiple myeloma is a malignancy of plasma cells; these cells accumulate in bone marrow and overproduce a monoclonal protein. Plasma cell malignancies include a spectrum of diseases, from monoclonal gammopathy of undetermined significance (MGUS) to smoldering multiple myeloma (SMM), clinical multiple myeloma, and, rarely, plasma cell leukemia. The disease process is insidious, with endorgan damage occurring over years.

Relapsed and refractory multiple myeloma (MM) constitutes a specific and unmet medical need. Median survival ranges from as little as 6 to 9 months, and responses to treatment are characteristically short. Patients with relapsed/refractory disease are defined as those who, having achieved minor response or better, relapse and then progress while on salvage therapy, or experience progression within 60 days of their last therapy. In the era prior to the development of novel biologically based therapies for MM, relapse from successive treatment regimens resulted in progressively shorter response durations, which typically reflected emerging drug resistance, as well as changes in disease biology within each patient, with tumor cells expressing a more aggressive phenotype, higher proliferative fraction and lower apoptotic rates.

Multiple myeloma accounts for 1.6% of all cancer cases and approximately 10% of hematologic malignancies in the United States. In 2015, there were an estimated 28,850 new cases of multiple myeloma diagnosed in the United States and more than 11,000 related deaths. The median age of presentation is 70 years; only 15% of patients diagnosed with multiple myeloma are younger than 65 years. Blacks have a twofold higher incidence compared with whites and present at a younger age. Cytogenetic abnormalities are detected in 90% of the plasma cells in patients with multiple myeloma, and multistep genetic alterations lead to the progression from MGUS to multiple myeloma in some persons.

Efficacy

The efficacy of ciltacabtagene autoleucel was evaluated in CARTITUDE-1 (NCT03548207), an open-label, single-arm, multicenter trial in adult patients with relapsed or refractory multiple myeloma, who previously received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Patients with known active or prior history of significant central nervous system (CNS) disease, including CNS multiple myeloma, plasma cell leukemia, allogeneic stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance <40 mL/min, absolute lymphocyte concentration <300/µL, absolute neutrophil count <750 cells/mm^3, platelet count <50,000/mm^3, hepatic

transaminases >3 times the upper limit of normal, cardiac ejection fraction <45%, or with active serious infection were excluded from the trial.

Of the 113 patients who underwent leukapheresis, 16 patients did not receive ciltacabtagene autoleucel due to progressive disease (n=2), death (n=9), or withdrawal from study (n=5). There were 97 patients in the efficacy evaluable population who received ciltacabtagene autoleucel, including 17 patients (18%) with manufacturing failures either because they received ciltacabtagene autoleucel that did not meet product release specifications for Carvykti™ or received ciltacabtagene autoleucel for which there were insufficient data to confirm product release specifications for Carvykti™.

Of the 97 efficacy-evaluable patients, the median age was 61 years (range: 43 to 78 years), 59% were male, 71% were white, and 18% were black. Most patients (86%) were International Staging System (ISS) Stage I or II. Of the 91 patients for whom baseline cytogentic data were available, high-risk cytogenetics (presence of t (4:14), t (14:16), or 17p13 del) were present in 24% of patients. Thirteen percent of the patients had extramedullary disease.

The median number of prior lines of therapy was 6 (range: 3 to 18), with 82% of patients receiving 4 or more prior lines of therapy, 90% of patients had received prior autologous stem cell transplantation (ASCT) and 8% of patients received an allogeneic transplant. Ninety-nine percent of patients were refractory to their last line of prior therapy, and 88% were refractory to a proteasome inhibitor (PI), immunomodulatory agent, and anti-CD38 antibody. Most patients (75%) treated with ciltacabtagene autoleucel received bridging therapy for control of their multiple myeloma during the manufacturing process. The median time from leukapheresis to product availability was 32 days (range: 27 to 66 days). The most commonly used agents as bridging therapies (≥20% of patients) included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), cyclophosphamide: 22 patients (23%), and pomalidomide: 21 patients (22%).

Efficacy was established on the basis of overall response rate, complete response rate and duration of response as assessed by the Independent Review Committee (IRC) using International Myeloma Working Group (IMWG) criteria (see Table). The median time to first response was 1 month (range: 0.9 to 10.7 months). The IRC assessed overall response in the 113 patients that underwent leukapheresis was 84% (95% CI: 76, 90) with stringent CR rate of 67% (95% CI: 58, 76), VGPR rate of 14% (95% CI: 8, 22) and PR rate of 3% (95% CI: 1, 8).

The most common (greater or equal to 10%) Grade 3 or 4 nonlaboratory adverse reactions were infections-pathogen unspecified (17%), pneumonia (11%), febrile neutropenia (10%), and hypotension (10%).

The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) included pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections of unspecified pathogen, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting.

Serious adverse reactions occurred in 55% of patients. The most common non-laboratory (greater than or equal to 5%) serious adverse reactions included CRS (21%), sepsis (7%), encephalopathy (10%), and pneumonia (7%). Fatal adverse reactions occurred in 9% of patients.

Table 1: Summary of efficacy results for CARTITUDE-1 based on IRC using IMWG criteria

	Ciltacabtagene autoleucel treated (N=97)
Overall Response Rate (sCR[a] + VGPR + PR) n (%)	95 (97.9)
95% CI (%)	(92.7, 99.7)
Stringent complete response (sCR)[a] n (%)	76 (78.4)
95% CI[b] (%)	(68.8, 86.1)
Very good partial response (VGPR) n (%)	16 (16.5)
95% CI[b] (%)	(9.7, 25.4)
Partial response (PR) n (%)	3 (3.1)
95% CI[b] (%)	(0.6, 8.8)
Duration of Response (DOR)	
Number of responders	95
DOR (Months):Median (95% CI)[c]	21.8 (21.8, NE)
Number of responders with sCR[a]	76
DOR if best response is sCR[a] (Months):Median (95% CI)[c]	NE (21.8, NE)
Number of responders with VGPR or better	92
DOR if best response is VGPR or better (Months):Median (95% CI)[c]	21.8 (21.8, NE)

Notes: Based on a median duration of follow-up of 18 months.

[a] All complete responses were stringent CRs.

[b] Exact 95% confidence interval.

[c] Kaplan-Meier estimate.

CI=confidence interval; IRC=Independent Review Committee; IMWG=International Myeloma Working Group; NE=not estimable.

Safety

ADVERSE EVENTS

The most common nonlaboratory adverse reactions (incidence greater than 20%) are pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. The most common laboratory adverse reactions (incidence greater than or equal to 50%) include thrombocytopenia, neutropenia, anemia, aminotransferase elevation and hypoalbuminemia.

WARNINGS & PRECAUTIONS

- Prolonged and Recurrent Cytopenias: Patients may exhibit ≥Grade 3 cytopenias following Carvykti™ infusion. One or more recurrences of Grade 3 or higher cytopenias may occur after partial or complete recovery of cytopenias. Monitor blood counts prior to and after Carvykti™ infusion. Prolonged neutropenia has been associated with increased risk of infection.
- Infections: Monitor patients for signs and symptoms of infection; treat appropriately.
- Hypogammaglobulinemia: Monitor and consider immunoglobulin replacement therapy.
- Hypersensitivity Reactions: Hypersensitivity reactions have occurred. Monitor for hypersensitivity reactions during infusion.
- Secondary Malignancies: Patients treated with Carvykti™ may develop secondary malignancies. Monitor life-long for secondary malignancies.
- Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving Carvykti™ and in the event of any new onset of neurologic toxicities.

CONTRAINDICATIONS

None reported

Clinical Pharmacology

MECHANISMS OF ACTION

Carvykti™ is a BCMA-directed, genetically modified autologous T cell immunotherapy, which involves reprogramming a patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) that identifies and eliminates cells that express BCMA. The Carvykti™ CAR protein features two BCMA-targeting single-domain antibodies designed to confer high avidity against human BCMA, a 4-1BB co-stimulatory domain and a CD3-zeta (CD3ζ) signaling cytoplasmic domain. Upon binding to BCMA-expressing cells, the CAR promotes T cell activation, expansion, and elimination of target cells.

Dose & Administration

ADULTS

$0.5–1.0\times10^{6}$ CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10^{8} CAR-positive viable T cells per single infusion.

For autologous use and intravenous use only:

- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of Carvykti™.
- Do not use a leukodepleting filter.
- Verify the patient's identity prior to infusion.
- Premedicate with acetaminophen and an H1-antihistamine.
- Avoid prophylactic use of systemic corticosteroids.
- Confirm availability of tocilizumab prior to infusion.
- Dosing of Carvykti™ is based on the number of chimeric antigen receptor (CAR)-positive viable T cells.

PEDIATRICS

None

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None

HEPATIC IMPAIRMENT

None

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

- Carvykti™ is a cell suspension for intravenous infusion.
- A single dose of Carvykti™ contains a cell suspension of 0.5–1.0×106 CAR-positive viable T cells per kg body weight in one infusion bag.