HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CARVYKTI safely and effectively. See full prescribing information for CARVYKTI.

CARVYKTI® (ciltacabtagene autoleucel) suspension for intravenous infusion
Initial U.S. Approval: 2022

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS and PROLONGED and RECURRENT CYTOPENIA

See full prescribing information for complete boxed warning.

- **Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI. Do not administer CARVYKTI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids. (2.2, 2.3, 5.1)**
- **Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI. Provide supportive care and/or corticosteroids as needed. (2.2, 2.3, 5.2)**
- **Parkinsonism and Guillain-Barré syndrome and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI. (5.2)**
- **Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI. HLH/MAS can occur with CRS or neurologic toxicities. (5.3)**
- **Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI. (5.5)**
- **CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS. (5.4)**

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions (5.1, 5.2, 5.3, 5.6)	02/2023

---------- INDICATIONS AND USAGE ----------

CARVYKTI is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. (1)

----------DOSAGE AND ADMINISTRATION----------

For autologous use only. For intravenous use only.

- Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of CARVYKTI. (2.2)
- Do NOT use a leukodepleting filter. (2.2)
- Verify the patient's identity prior to infusion. (2.2)
- Premedicate with acetaminophen and an H1-antihistamine. (2.2)
- Avoid prophylactic use of systemic corticosteroids. (2.2)
- Confirm availability of tocilizumab prior to infusion. (2.2, 5.1)
- Dosing of CARVYKTI is based on the number of chimeric antigen receptor (CAR)-positive viable T cells. (2.1)
- Recommended dose range is 0.5-1.0×10^6 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-dose infusion. (2.1)
- Administer CARVYKTI at a REMS-certified healthcare facility. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

- CARVYKTI is a cell suspension for intravenous infusion. (3)
- A single dose of CARVYKTI contains a cell suspension of 0.5-1.0×10^6 CAR-positive viable T cells per kg body weight in one infusion bag. (3)

---------- CONTRAINDICATIONS ----------

None (4)

---------- WARNINGS AND 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. (5.5)
- Infections: Monitor patients for signs and symptoms of infection; treat appropriately. (5.6)
- Hypogammaglobulinemia: Monitor and consider immunoglobulin replacement therapy. (5.7)
- Hypersensitivity Reactions: Hypersensitivity reactions have occurred. Monitor for hypersensitivity reactions during infusion. (5.8)
- Secondary Malignancies: In the event that a secondary malignancy occurs after treatment with CARVYKTI, contact Janssen Biotech, Inc. at 1-800-526-7736. (5.9)
- 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. (5.10)

---------- ADVERSE REACTIONS ----------

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. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS and PROLONGED and RECURRENT CYTOPENIA

Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVYKTI. Do not administer CARVYKTI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.1)]*.

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), which may be fatal or life-threatening, occurred following treatment with CARVYKTI, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVYKTI. Provide supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.2, 2.3), Warnings and Precautions (5.2)]*.

Parkinsonism and Guillain-Barré syndrome and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI *[see Warnings and Precautions (5.2)]*.

Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVYKTI. HLH/MAS can occur with CRS or neurologic toxicities *[see Warnings and Precautions (5.3)]*.

Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI *[see Warnings and Precautions (5.5)]*.

CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS Program *[see Warnings and Precautions (5.4)]*.

1 INDICATIONS AND USAGE

CARVYKTI is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

2 DOSAGE AND ADMINISTRATION

For autologous use only. For intravenous use only.

2.1 Dose

CARVYKTI is provided as a single dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T cells in one infusion bag.

The recommended dose range is 0.5-1.0×10^6 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.

2.2 Administration

CARVYKTI is for autologous use only. The patient's identity must match the patient identifiers on the CARVYKTI cassette and infusion bag. Do not infuse CARVYKTI if the information on the patient-specific labels does not match the intended patient.

Preparing the Patient for CARVYKTI Infusion

Confirm availability of CARVYKTI prior to starting the lymphodepleting chemotherapy regimen.

Pretreatment

Administer the lymphodepleting chemotherapy regimen: cyclophosphamide 300 mg/m^2 intravenously (IV) and fludarabine 30 mg/m^2 IV daily for 3 days.

See the prescribing information of cyclophosphamide and fludarabine for information on dose adjustment in renal impairment.

Lymphodepleting regimen must be delayed if a patient has serious adverse reactions from preceding bridging therapies (including clinically significant active infection, cardiac toxicity, and pulmonary toxicity) or active graft versus host disease in patient with prior allogeneic stem cell transplant. Consider repeating lymphodepleting regimen if CARVYKTI dosing is delayed by more than 14 days and patient has recovered from toxicity of the first lymphodepleting regimen.

Administer CARVYKTI infusion 2 to 4 days after the completion of the lymphodepleting chemotherapy regimen.

CARVYKTI infusion should be delayed if a patient has any of the following conditions:

- Clinically significant active infection or inflammatory disorders.
- Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning, except for Grade 3 nausea, vomiting, diarrhea, or constipation. CARVYKTI infusion should be delayed until resolution of these events to Grade ≤1.

Premedication

Administer the following pre-infusion medications to all patients 30 - 60 minutes prior to CARVYKTI infusion:

CARVYKTI® (ciltacabtagene autoleucel)

- Antipyretics (oral or intravenous acetaminophen 650 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Avoid prophylactic use of systemic corticosteroids, because their use may interfere with the activity of CARVYKTI.

Receipt of CARVYKTI

- All sites approved for infusion will support required storage conditions for vapor phase of liquid nitrogen.
- CARVYKTI is shipped directly to the cell laboratory or clinical pharmacy associated with the infusion center in the vapor phase of a liquid nitrogen shipper.
- Confirm the patient's identity with the patient identifiers on the shipper.
- If the patient is not expected to be ready for same-day administration, before the shipper expires, transfer CARVYKTI to onsite vapor phase of liquid nitrogen storage.

Preparation of CARVYKTI for Infusion

Do not thaw the product until it is ready to be used. Coordinate the timing of CARVYKTI thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that CARVYKTI is available for infusion when the patient is ready. Once thawed, the CARVYKTI infusion must be completed within 2.5 hours at room/ambient temperature (20°C to 25°C).

Prior to thawing the product, confirm that tocilizumab and emergency equipment are available prior to the infusion and during the recovery period.

1. Confirm patient identity: Prior to CARVYKTI preparation, match the patient's identity with the patient identifiers on the CARVYKTI cassette. Do not remove the CARVYKTI infusion bag from the cassette if the information on the patient-specific label does not match the intended patient. Contact **Janssen Biotech, Inc.** at **1-800-526-7736** if there are any discrepancies between the labels and the patient identifiers.
2. Once patient identification is confirmed, remove the CARVYKTI product bag from the cassette and check that the patient information on the cassette label matches the patient information on the bag label.
3. Inspect the product bag for any breaches of container integrity, such as breaks or cracks before thawing. Do not administer if the bag is compromised, and contact **Janssen Biotech, Inc.** at **1-800-526-7736.**
4. Place the infusion bag inside a sealable plastic bag (preferably sterile) prior to thawing.
5. Thaw CARVYKTI at 37°C±2°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Total time from start of thaw until completion of thawing should be no more than 15 minutes.
6. Remove the infusion bag from the sealable plastic bag and wipe dry. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Do not pre-filter into a different container, wash, spin down, or resuspend CARVYKTI in new media prior to infusion.
7. Do not re-freeze or refrigerate thawed product.

Administration

- For autologous infusion only.
- Do NOT use a leukocyte-depleting filter.
- Ensure that a minimum of two doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period.
- Central venous access may be utilized for the infusion of CARVYKTI and is encouraged in patients with poor peripheral access.

1. Confirm the patient's identity with the patient identifiers on the infusion bag. Do not infuse CARVYKTI if the information on the patient-specific label does not match the intended patient.
2. Prime the tubing of the infusion set with normal saline prior to infusion.
3. Once thawed, administer the entire contents of the CARVYKTI bag by intravenous infusion within 2.5 hours using infusion sets fitted with an in-line filter.
4. Gently mix the contents of the bag during CARVYKTI infusion to disperse cell clumps.
5. After the entire content of the product bag is infused, flush the administration line, inclusive of the in-line filter, with normal saline with a volume equal or greater to the total hold up volume of the primary administration set used inclusive of the drip tube, to ensure that all product is delivered.

CARVYKTI contains human blood cells that are genetically modified with replication-incompetent, self-inactivating, lentiviral vector. Follow universal precautions and local biosafety guidelines for handling and disposal of CARVYKTI to avoid potential transmission of infectious diseases.

Monitoring After Infusion

Administer CARVYKTI at a REMS-certified healthcare facility.

Monitor patients at least daily for 10 days following CARVYKTI infusion at a certified healthcare facility for signs and symptoms of cytokine release syndrome (CRS) and

neurologic toxicities. Monitor periodically for 4 weeks for signs and symptoms of delayed neurologic toxicity.

Instruct patients to remain within proximity of a certified healthcare facility for at least 4 weeks following infusion.

Instruct patients to refrain from driving or hazardous activities for at least 8 weeks following infusion.

2.3 Management of Severe Adverse Reactions

Cytokine Release Syndrome

Identify CRS based on clinical presentation *[see Warnings and Precautions (5.1)]*. Evaluate for and treat other causes of fever, hypoxia and hypotension. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. If CRS is suspected, manage according to the recommendations in Table 1.

Patients who experience CRS should be closely monitored for cardiac and other organ function until resolution of symptoms. Consider anti-seizure prophylaxis with levetiracetam in patients who experience CRS.

Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous telemetry and pulse oximetry.

For severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy.

For CRS refractory to first line interventions such as tocilizumab or tocilizumab and corticosteroids, consider alternate treatment options (i.e., higher corticosteroid dose, alternative anti-cytokine agents, e.g., anti-IL1 and/or anti-TNFα, anti-T cell therapies). Refractory CRS is characterized by fevers, end-organ toxicity (e.g., hypoxia, hypotension) not improving within 12 hours of first line interventions or development of HLH/MAS.

If concurrent neurologic toxicity is suspected during CRS, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Anti-seizure medication according to the neurologic toxicity in Table 2

Table 1: CRS Grading and Management Guidance

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
Grade 1 Temperature ≥38°C[c]	In patients with: • Early onset of fever (if onset less than 72 hours after infusion) Tocilizumab 8 mg/kg intravenously (IV) over 1 hour (not to exceed 800 mg) may be considered	N/A
Grade 2 Symptoms require and respond to moderate intervention. Temperature ≥38°C[c] with: Hypotension not requiring vasopressors, and/or, Hypoxia requiring oxygen via canula[e] or blow-by, or, Grade 2 organ toxicity.[g]	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids up to 1 liter or increasing supplemental oxygen.	Consider dexamethasone 10 mg IV every 12-24 hours.
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours. After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	

Table 1: CRS Grading and Management Guidance (continued)

CRS Grade[a]	Tocilizumab[b]	Corticosteroids[f]
Grade 3 Symptoms require and respond to aggressive intervention.	Per Grade 2	Administer dexamethasone 10 mg IV every 12 hours.
Temperature ≥38°C[c] with: Hypotension requiring one vasopressor with or without vasopressin, and/or, Hypoxia requiring oxygen via high-flow nasal canula[e], facemask, non-rebreather mask, or Venturi mask, or, Grade 3 organ toxicity or Grade 4 transaminitis.	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours. After 2 doses of tocilizumab, consider alternative anti-cytokine agents.[d] Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.	
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD). Temperature ≥38°C[c] with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2	Administer dexamethasone 20 mg IV every 6 hours.
	After 2 doses of tocilizumab, consider alternative anti-cytokine agents[d]. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total. If no improvement within 24 hours, consider methylprednisolone (1-2 g IV, repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (e.g. other anti-T cell therapies).	

[a] Based on ASTCT 2019 grading system (Lee et.al, 2019), modified to include organ toxicity.
[b] Refer to tocilizumab prescribing information for details.
[c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (e.g., tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause.
[d] Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
[e] Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.
[f] Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days.
[g] Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0.

Neurologic Toxicities

Monitor patients for signs and symptoms of neurologic toxicities (ICANS and other neurologic toxicities) (Table 2). Rule out other causes of neurologic signs or symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities. Please see section 5.2 for non ICANS neurologic toxicities. If ICANS is suspected, manage according to the recommendations in Table 2.

If concurrent CRS is suspected during the neurologic toxicity event, administer:

- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to CRS grade in Table 1
- Anti-seizure medication according to neurologic toxicity in Table 2

Table 2: Guideline for management of ICANS

ICANS Grade[a]	Corticosteroids
Grade 1 ICE score 7-9[b] or depressed level of consciousness: awakens spontaneously.	Consider dexamethasone[c] 10 mg IV every 12 to 24 hours for 2 to 3 days. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 2 ICE score-3-6[b] or depressed level of consciousness: awakens to voice	Administer dexamethasone[c] 10 mg IV every 12 hours for 2-3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 3 days. If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.
Grade 3 ICE score-0-2[b] (If ICE score is 0, but the patient is arousable (e.g., awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local edema on neuroimaging[d].	Administer dexamethasone[c] 10 mg-20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate dexamethasone[c] dose to at least 20 mg IV every 6 hours, OR escalate to high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated) Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated).
Grade 4 ICE score-0[b] (Patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures, either: • life-threatening prolonged seizure (>5 min), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[e]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP/cerebral edema, with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad	Administer dexamethasone[c] 20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2 g/day, repeated every 24 hours if needed; taper as clinically indicated). Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation.

Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.

[a] ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et.al, 2019).

[b] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point); and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.

[c] All references to dexamethasone administration are dexamethasone or equivalent.

[d] Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to NCI CTCAE v5.0.

[e] Tremors and myoclonus associated with immune effector cell therapies may be graded according to NCI CTCAE v5.0, but they do not influence ICANS grading.

3 DOSAGE FORMS AND STRENGTHS

CARVYKTI is a cell suspension for intravenous infusion.

A single dose of CARVYKTI contains a cell suspension of 0.5-1.0×10^6 CAR-positive viable T cells per kg body weight in one infusion bag up to a maximum of 1×10^8 CAR-positive viable T cells *[see How Supplied/Storage and Handling (16)]*.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

Cytokine release syndrome, including fatal or life-threatening reactions, occurred following treatment with CARVYKTI. CRS occurred in 95% (92/97) of patients receiving ciltacabtagene autoleucel. Grade 3 or higher CRS (2019 ASTCT grade)[1] occurred in 5% (5/97) of patients, with Grade 5 CRS reported in 1 patient. The median time to onset of CRS was 7 days (range: 1 to 12 days). The median duration of CRS was 4 days (range:1 to 40 days) in all but one patient who had a duration of CRS of 97 days with a subsequent fatal outcome. In patients who experienced CRS, the most common manifestations of CRS included pyrexia (100%), hypotension (43%), increased aspartate aminotransferase (AST) (22%), chills (15%), increased alanine aminotransferase (ALT) (14%) and sinus tachycardia (11%). Grade 3 or higher events associated with CRS included increased AST and ALT, hyperbilirubinemia, hypotension, pyrexia, hypoxia, respiratory failure, acute kidney injury, disseminated intravascular coagulation and hemorrhage, HLH/MAS, angina pectoris, supraventricular and ventricular tachycardia, malaise, myalgias, increased-C-reactive protein, ferritin, blood alkaline phosphatase and gamma-glutamyl transferase *[see Adverse Reactions (6.1)]*.

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS. One patient with CRS and suspected HLH/MAS developed a fatal retroperitoneal hemorrhage in the setting of thrombocytopenia, coagulopathy and anticoagulation in another ongoing study of CARVYKTI. Please see Section 5.3; Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS).

Sixty-nine of 97 (71%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of ciltacabtagene autoleucel. Forty-four (45%) patients received tocilizumab without corticosteroids, of whom 33 (34%) received a single dose and 11 (11%) received more than 1 dose; 24 patients (25%) received tocilizumab and a corticosteroid, and one patient (1%) received only corticosteroids.

Ensure that a minimum of two doses of tocilizumab are available prior to infusion of CARVYKTI.

Monitor patients at least daily for 10 days following CARVYKTI infusion at a REMS-certified healthcare facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, as indicated in Table 1 *[see Dosing and Administration (2.3)]*.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time *[see Patient Counseling information (17)]*.

5.2 Neurologic Toxicities

Neurologic toxicities, which may be severe, life-threatening or fatal, occurred following treatment with CARVYKTI. Neurologic toxicities included ICANS, neurologic toxicity with signs and symptoms of parkinsonism, Guillain-Barré Syndrome, immune mediated myelitis, peripheral neuropathies and cranial nerve palsies. Counsel patients on the signs and symptoms of these neurologic toxicities, and on the delayed nature of onset of some of these toxicities. Instruct patients to seek immediate medical attention for further assessment and management if signs or symptoms of any of these neurologic toxicities occur at any time *[see Patient Counseling Information (17)]*.

Overall, one or more subtypes of neurologic toxicity[2] described below occurred following ciltacabtagene autoleucel infusion in 26% (25/97) of patients of which

11% (11/97) of patients experienced Grade 3 or higher events. These subtypes of neurologic toxicities were also observed in 2 ongoing studies *[see Adverse Reactions (6.1)]*.

Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

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 ciltacabtagene autoleucel including Grade 3 or 4 events in 3% (3/97) and Grade 5 (fatal) events in 2% (2/97). Two patients had ongoing Grade 3 and Grade 1 ICANS at last known alive date and one patient had Grade 1 ICANS ongoing at time of death from neurologic toxicity with parkinsonian features. The median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 17 of 22 patients (77%), and the median time to resolution was 6 days (range: 2 to 143 days). Median duration of ICANS in all patients, including those with fatal ICANS, ICANS ongoing at time of death from other causes or ongoing at last known alive date, was 7.5 days (range: 2 to 927 days). All 22 patients with ICANS had CRS. The onset of ICANS occurred during CRS in 16 patients, before the onset of CRS in 3 patients, and after the CRS event in 3 patients.

The most frequent (≥5%) manifestation of ICANS included encephalopathy (23%), aphasia (8%) and headache (6%).

Monitor patients at least daily for 10 days following CARVYKTI infusion at the REMS-certified healthcare facility for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 4 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed *[see Dosage and Administration (2.3)]*.

Parkinsonism

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. Neurologic toxicity with parkinsonism has been reported in other ongoing trials of ciltacabtagene autoleucel. Patients had parkinsonian and non-parkinsonian symptoms that included tremor, bradykinesia, involuntary movements, stereotypy, loss of spontaneous movements, masked facies, apathy, flat affect, fatigue, rigidity, psychomotor retardation, micrographia, dysgraphia, apraxia, lethargy, confusion, somnolence, loss of consciousness, delayed reflexes, hyperreflexia, memory loss, difficulty swallowing, bowel incontinence, falls, stooped posture, shuffling gait, muscle weakness and wasting, motor dysfunction, motor and sensory loss, akinetic mutism and frontal lobe release signs. Symptoms did not respond to one or more of the following treatments attempted in one or more patients – systemic chemotherapy, intrathecal chemotherapy and steroids, dopaminergic agents, systemic corticosteroids, plasmapheresis, and intravenous immunoglobulin and dasatinib. One patient experienced partial resolution with residual gait disturbance without treatment for parkinsonism, immunosuppressants or chemotherapy. The median onset of parkinsonism in the 5 patients in CARTITUDE-1 was 43 days (range: 15 to 108 days) from infusion of ciltacabtagene autoleucel. One patient died of neurologic toxicity with parkinsonism 247 days after administration of ciltacabtagene autoleucel; two patients with ongoing parkinsonism died of infectious causes 162 and 119 days after administration of ciltacabtagene autoleucel; in the remaining 2 patients, symptoms of parkinsonism were ongoing up to 530 days after administration of ciltacabtagene autoleucel. Maximum toxicity grade was 2, 3, 4 and 5 in 1, 2, 1 and 1 patient respectively. All 5 patients had a history of prior CRS (n=4 Grade 2; n=1 Grade 3), while 4 of 5 patients had prior ICANS (n=4 Grade 1).

Monitor patients for signs and symptoms of parkinsonism that may be delayed in onset and managed with supportive care measures. There is limited efficacy information with medications used for the treatment of Parkinson's disease for the improvement or resolution of parkinsonism symptoms following CARVYKTI treatment.

Guillain-Barré Syndrome

A fatal outcome following Guillain-Barré Syndrome (GBS) has occurred in another ongoing study of ciltacabtagene autoleucel despite treatment with intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

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.

Immune Mediated Myelitis

Grade 3 myelitis has occurred 25 days following treatment with CARVYKTI in another ongoing study. Symptoms reported included hypoesthesia of the lower extremities and the lower abdomen with impaired sphincter control. Symptoms improved with the use of corticosteroids and intravenous immune globulin. Myelitis was ongoing at the time of death from other cause.

Peripheral Neuropathy

Six patients in CARTITUDE-1 developed peripheral neuropathy. These neuropathies presented as sensory, motor or sensorimotor neuropathies. Median time of onset of symptoms was 62 days (range: 4 to 136 days), median duration of peripheral neuropathies was 256 days (range: 2 to 465 days) including those with ongoing neuropathy. Of these six patients, two patients experienced Grade 3 peripheral neuropathy, and 3 had resolution of neuropathy. Treatment with corticosteroids in one patient was not associated with improvement of peripheral neuropathy. Patients who experienced peripheral neuropathy also experienced cranial nerve palsies or GBS in other ongoing trials of ciltacabtagene autoleucel.

CARVYKTI® (ciltacabtagene autoleucel)

Monitor patients for signs and symptoms of peripheral neuropathies.

Cranial Nerve Palsies

Three patients (3.1%) experienced cranial nerve palsies in CARTITUDE-1. All 3 patients had 7th cranial nerve palsy; one patient had 5th cranial nerve palsy as well. Median time to onset was 26 days (range: 21 to 101 days) following infusion of ciltacabtagene autoleucel. All three patients received systemic corticosteroids and had resolution of symptoms; one patient received valacyclovir in addition to corticosteroids. Median time to resolution was 70 days (range: 1 to 79 days) following onset of symptoms. Occurrence of 3rd and 6th cranial nerve palsy, bilateral 7th cranial nerve palsy, worsening of cranial nerve palsy after improvement and occurrence of peripheral neuropathy in patients with cranial nerve palsy have also been reported in ongoing trials of ciltacabtagene autoleucel.

Monitor patients for signs and symptoms of cranial nerve palsies. Consider management with systemic corticosteroids, depending on the severity and progression of signs and symptoms.

5.3 Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS)

Fatal HLH occurred in one patient (1%), 99 days after ciltacabtagene autoleucel infusion. The HLH event was preceded by prolonged CRS lasting 97 days.

The manifestations of HLH/MAS include hypotension, hypoxia with diffuse alveolar damage, coagulopathy, cytopenia and multi-organ dysfunction, including renal dysfunction.

One patient with grade 4 HLH/MAS developed fatal intracerebral and gastrointestinal hemorrhage in the setting of coagulopathy and thrombocytopenia 12 days after treatment in another ongoing study of CARVYKTI *[see Warnings and Precautions (5.1)]*. Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematological parameters in patients with HLH/MAS and transfuse per institutional guidelines.

HLH is a life-threatening condition with a high mortality rate if not recognized and treated early. Treatment of HLH/MAS should be administered per institutional standards.

5.4 CARVYKTI REMS

Because of the risk of CRS and neurologic toxicities, CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*. The required components of the CARVYKTI REMS are:

- Healthcare facilities that dispense and administer CARVYKTI must be enrolled and comply with the REMS requirements.
- Certified healthcare facilities must have on-site, immediate access to tocilizumab.
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after CARVYKTI infusion, if needed for treatment of CRS.
- Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer CARVYKTI are trained in the management of CRS and neurologic toxicities.

Further information is available at www.carvyktirems.com or 1-844-672-0067.

5.5 Prolonged and Recurrent Cytopenias

Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI infusion. In Study CARTITUDE-1 (N=97), 30% (29/97) of patients experienced prolonged Grade 3 or 4 neutropenia and 41% (40/97) of patients experienced prolonged Grade 3 or 4 thrombocytopenia that had not resolved by Day 30 following ciltacabtagene autoleucel infusion. In 31% (29/95) of patients who recovered from Grade 3 or 4 neutropenia after 1 month, the median time to recovery from ciltacabtagene autoleucel infusion was 1.8 months (range: 1.0 to 3.7 months). In 52% (32/61) of patients who recovered from Grade 3 or 4 thrombocytopenia after 1 month, the median time to recovery from ciltacabtagene autoleucel infusion was 1.9 months (range: 1.1 to 8.5 months).

One patient underwent autologous stem cell therapy for hematopoietic reconstitution due to prolonged thrombocytopenia.

Recurrent Grade 3 or 4 neutropenia, thrombocytopenia, lymphopenia, and anemia were seen in 63% (61/97), 18% (17/97), 60% (58/97), and 37% (36/97) after recovery from initial Grade 3 or 4 cytopenia following ciltacabtagene autoleucel infusion. After Day 60 following ciltacabtagene autoleucel, 31%, 12%, and 6% of patients had a recurrence of Grade 3 or higher lymphopenia, neutropenia, and thrombocytopenia, respectively, after initial recovery of their Grade 3 or 4 cytopenia *[see Adverse Reactions (6.1)]*. Eighty-seven percent (84/97) of patients had one, two or three or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia. Six and 11 patients had Grade 3 or 4 neutropenia and thrombocytopenia respectively at the time of death.

Monitor blood counts prior to and after CARVYKTI infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines.

5.6 Infections

CARVYKTI should not be administered to patients with active infection or inflammatory disorders. Severe, life-threatening, or fatal infections, occurred in patients after CARVYKTI infusion *[see Adverse Reactions (6.1)]*.

Infections (all grades) occurred in 57 (59%) patients. Grade 3 or 4 infections occurred in 23% (22/97) of patients; Grade 3 or 4 infections with an unspecified pathogen occurred in 17%, viral infections in 7%, bacterial infections in 1%, and

fungal infections in 1% of patients. Overall, 4 patients had Grade 5 infections: lung abscess (n=1), sepsis (n=2) and pneumonia (n=1).

Grade 5 infections reported in other studies with CARVYKTI include bronchopulmonary aspergillosis, pneumocystis jirovecii pneumonia, and CMV colitis (with HSV-1 hepatitis). Another patient developed mycotic aneurysm due to cerebral aspergillosis and died of subarachnoid hemorrhage.

Monitor patients for signs and symptoms of infection before and after CARVYKTI infusion and treat patients appropriately. Administer prophylactic, pre-emptive and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 10% of patients after ciltacabtagene autoleucel infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

In a randomized controlled study of relapsed or refractory multiple myeloma (CARTITUDE- 4), patients treated with ciltacabtagene autoleucel had an increased rate of fatal COVID-19 infections compared to the standard therapy arm. Counsel patients on the importance of prevention measures. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID 19.

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia.

Perform screening for Cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing.

Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

5.7 Hypogammaglobulinemia

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI. Hypogammaglobulinemia was reported as an adverse event in 12% (12/97) of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 92% (89/97) of patients treated with ciltacabtagene autoleucel. Hypogammaglobulinemia either as an adverse reaction or a laboratory IgG level below 500 mg/dL, after infusion occurred in 94% (91/97) of patients treated with ciltacabtagene autoleucel. Thirty-eight percent of patients received intravenous immunoglobulin (IVIG) post ciltacabtagene autoleucel for either an adverse reaction or prophylaxis.

Monitor immunoglobulin levels after treatment with CARVYKTI and administer IVIG for IgG <400 mg/dL. Manage per local institutional guidelines, including infection precautions and antibiotic or antiviral prophylaxis.

Use of Live Vaccines

The safety of immunization with live viral vaccines during or following CARVYKTI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during CARVYKTI treatment, and until immune recovery following treatment with CARVYKTI.

5.8 Hypersensitivity Reactions

Hypersensitivity reactions have occurred in 5% (5/97) of patients following ciltacabtagene autoleucel infusion. All reactions were Grade 1 and symptoms included flushing (n=4), chest discomfort (n=2), tachycardia (n=1), wheezing (n=1), tremor (n=1), and burning sensation (n=1). Serious hypersensitivity reactions, including anaphylaxis, may be due to the dimethyl sulfoxide (DMSO) in CARVYKTI. Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of severe reaction. Treat promptly and manage patients appropriately according to the severity of the hypersensitivity reaction.

5.9 Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies. Monitor life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact Janssen Biotech, Inc. at 1-800-526-7736 for reporting and to obtain instructions on collection of patient samples for testing of secondary malignancy of T cell origin.

5.10 Effects on Ability to Drive and Use Machines

Due to the potential for neurologic events, including altered mental status, seizures, neurocognitive decline or neuropathy, patients receiving CARVYKTI are at risk for altered or decreased consciousness or coordination in the 8 weeks following CARVYKTI infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery during this initial period, and in the event of new onset of any neurologic toxicities.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are also described elsewhere in the labeling:

- Cytokine Release Syndrome *[see Warnings and Precautions (5.1)]*.
- Neurologic Toxicities *[see Warnings and Precautions (5.2)]*.
- Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) *[see Warnings and Precautions (5.3)]*.
- Prolonged and Recurrent Cytopenias *[see Warnings and Precautions (5.5)]*.
- Infections *[see Warnings and Precautions (5.6)]*.
- Hypogammaglobulinemia *[see Warnings and Precautions (5.7)]*.
- Hypersensitivity Reactions *[see Warnings and Precautions (5.8)]*.

CARVYKTI® (ciltacabtagene autoleucel)

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect the exposure of 97 adult patients with relapsed/refractory multiple myeloma in the CARTITUDE-1 study (USA cohort) to ciltacabtagene autoleucel and includes 17 patients (18%) with manufacturing failures either because they received ciltacabtagene autoleucel that did not meet product release specifications or there were insufficient data to confirm product release specifications for CARVYKTI. Patients received ciltacabtagene autoleucel across a dose range of 0.51 to 0.95×10^6 CAR-positive viable T cells/kg body weight *[see Clinical Studies (14)]*. Patients with a history of CNS disease (such as seizure or cerebrovascular ischemia) or requiring ongoing treatment with chronic immunosuppression were excluded. The median duration of follow-up was 18 months. The median age of the study population was 61 years (range: 43 to 78 years); 36% were 65 years or older, and 59% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 40%, 1 in 56%, and 2 in 4% of patients. Three of the patients treated with ciltacabtagene autoleucel had a creatinine clearance of <45 mL/min at baseline. For the details about the study population, see *Clinical Studies (14)*.

The safety data in the *Warnings and Precautions* section also reflects exposure to ciltacabtagene autoleucel in two ongoing, open-label studies, including patients with previously untreated and relapsed/refractory multiple myeloma in a non-randomized, multi-cohort study (CARTITUDE-2) and patients with relapsed/refractory multiple myeloma in a randomized controlled study (CARTITUDE-4).

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 3 summarizes the adverse reactions that occurred in at least 10% of patients treated with ciltacabtagene autoleucel.

Table 4 describes the most common Grade 3 or 4 laboratory abnormalities.

Table 3: Adverse reactions observed in at least 10% of patients treated with ciltacabtagene autoleucel in CARTITUDE-1 Study (N=97)

System Organ Class (SOC) Preferred term	Any Grade (%)	Grade 3 or higher (%)
Blood and lymphatic system disorders		
Coagulopathy[a]	22	2.1
Febrile Neutropenia	10	10
Cardiac disorders		
Tachycardia[b]	27	1
Gastrointestinal disorders		
Diarrhea[c]	33	1
Nausea	31	1
Constipation	22	0
Vomiting	20	0
General disorders and administrative site conditions		
Pyrexia	96	5
Fatigue[d]	47	7
Chills	33	0
Edema[e]	23	0
Immune system disorders		
Cytokine release syndrome[f]	95	5
Hypogammaglobulinemia[g]	94	2
Infections and infestations[h]		
Infections-pathogen unspecified[i]	41	17
Upper respiratory tract infection[j]	28	3
Viral infections[k]	23	7
Pneumonia[l]	12	11
Sepsis[m]	10	7
Bacterial infections[n]	10	3
Metabolism and nutrition disorders		
Decreased appetite	29	1

Table 3: Adverse reactions observed in at least 10% of patients treated with ciltacabtagene autoleucel in CARTITUDE-1 Study (N=97) (continued)

System Organ Class (SOC) Preferred term	Any Grade (%)	Grade 3 or higher (%)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[o]	48	2
Nervous system disorders		
Encephalopathy[p]	30	6
Headache	27	0
Dizziness[q]	23	1
Motor dysfunction[r]	16	3
Psychiatric disorders		
Insomnia	13	0
Respiratory, thoracic and mediastinal disorders		
Cough[s]	39	0
Dyspnea[t]	23	3
Nasal congestion	15	0
Hypoxia	12	4
Vascular disorders		
Hypotension[u]	51	10
Hypertension	19	6
Hemorrhage[v]	15	4

Adverse reactions are reported using MedDRA version 23.0

[a] Coagulopathy includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Hypofibrinogenemia, International normalized ratio increased, and Prothrombin time prolonged. Also includes terms reported under investigation SOC.

[b] Tachycardia includes Sinus tachycardia, and Tachycardia.

[c] Diarrhea includes Colitis, and Diarrhea.

[d] Fatigue includes Asthenia, Fatigue, and Malaise.

[e] Edema includes Face edema, Generalized edema, Localized edema, Edema peripheral, Periorbital edema, Peripheral swelling, Pulmonary edema, and Scrotal edema.

[f] Cytokine release syndrome includes Cytokine release syndrome, and Systemic inflammatory response syndrome.

[g] Hypogammaglobulinemia includes subjects with adverse event of hypogammaglobulinemia (12%) and/or laboratory IgG levels that fell below 500 mg/dL following CARVYKTI infusion (92%).

[h] Infections and infestations System Organ Class Adverse Events are grouped by pathogen type and selected clinical syndromes.

[i] Infections - pathogen unspecified includes Abscess limb, Atypical pneumonia, Bacteremia, Bronchitis, Conjunctivitis, Enterocolitis infectious, Folliculitis, Gastroenteritis, Lung abscess, Lung opacity, Osteomyelitis, Otitis media, Parotitis, Perirectal abscess, Pneumonia, Rash pustular, Rhinitis, Sepsis, Septic shock, Sinusitis, Skin infection, Soft tissue infection, Tooth infection, Upper respiratory tract infection, and Urinary tract infection.

[j] Upper respiratory tract infection includes Human rhinovirus test positive, Rhinitis, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, and Viral upper respiratory tract infection. Also includes terms reported under investigation SOC. Upper respiratory tract infections may also be included under pathogen categories.

[k] Viral infection includes Adenovirus test positive, Coronavirus infection, Cytomegalovirus syndrome, Cytomegalovirus viremia, Enterovirus infection, Gastroenteritis viral, Herpes zoster, Herpes zoster disseminated, Influenza, Influenza like illness, Oral herpes, Parainfluenza virus infection, Rhinovirus infection, Urinary tract infection viral, and Viral upper respiratory tract infection.

[l] Pneumonia includes Atypical pneumonia, Lung abscess, Lung opacity, Pneumocystis jirovecii pneumonia, Pneumonia, and Pneumonia aspiration.

[m] Sepsis includes Bacteremia, Bacterial sepsis, Pseudomonal bacteremia, Sepsis, Septic shock, and Staphylococcal bacteremia.

[n] Bacterial infection includes Abscess limb, Cholecystitis, Cholecystitis acute, Clostridium difficile colitis, Clostridium difficile infection, Enterocolitis bacterial, Osteomyelitis, Perirectal abscess, Soft tissue infection, Staphylococcal infection, and Tooth infection.

[o] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Joint stiffness, Muscle strain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, and Pain in extremity.

[p] Encephalopathy includes Amnesia, Bradyphrenia, Confusional state, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Immune effector cell-associated neurotoxicity syndrome, Lethargy, Memory impairment, Mental impairment, Mental status changes, Noninfective encephalitis, and Somnolence.

[q] Dizziness includes Dizziness, Presyncope, and Syncope.

[r] Motor dysfunction includes Motor dysfunction, Muscle spasms, Muscle tightness, Muscular weakness, and Myoclonus.

[s] Cough includes Cough, Productive cough, and Upper-airway cough syndrome.

[t] Dyspnea includes Acute respiratory failure, Dyspnea, Dyspnea exertional, Respiratory failure, and Tachypnea.

CARVYKTI® (ciltacabtagene autoleucel)

[u] Hypotension includes Hypotension, and Orthostatic hypotension.

[v] Hemorrhage includes Conjunctival hemorrhage, Contusion, Ecchymosis, Epistaxis, Eye contusion, Hematochezia, Hemoptysis, Infusion site hematoma, Oral contusion, Petechiae, Post procedural hemorrhage, Pulmonary hemorrhage, Retinal hemorrhage, and Subdural hematoma.

Other clinically important adverse reactions that occurred in less than 10% of patients treated with ciltacabtagene autoleucel include the following:

- *Cardiac disorders:* cardiac arrhythmias[a] (8%), chest pain[b] (7%)
- *Eye disorders:* diplopia (1%)
- *Gastrointestinal disorders:* dysphagia (1%)
- *Immune system disorders:* hemophagocytic lymphohistiocytosis (1%), hypersensitivity reaction (5%)
- *Infections and Infestations:* urinary tract infection[c] (4.1%)
- *Injury, Poisoning and Procedural complications:* fall (3.1%)
- *Metabolism and Nutrition Disorders:* tumor lysis syndrome (1%)
- *Musculoskeletal and Connective tissue disorders:* posture abnormal (1%)
- *Nervous system disorders:* aphasia[d] (8%), ataxia[e] (8%), tremor (6%), peripheral neuropathy (6%), parkinsonism (4.1%), micrographia (4.1%), dysgraphia (3.1%), reduced facial expression (3.1%), cranial nerve palsies (3.1%), bradykinesia (2.1%), paresis[f] (1%), cogwheel rigidity (1%), cerebrovascular accident (1%), seizure (1%), low speech (1%), nystagmus (1%)
- *Psychiatric disorders:* delirium[g] (5%) depression[h] (4.1%), psychomotor retardation (1%)
- *Renal and urinary disorders:* renal failure[i] (7%)
- *Skin and subcutaneous tissues:* rash[j] (8%)
- *Vascular Disorders:* thrombosis[k] (5%)

[a] Cardiac arrhythmias includes atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia.

[b] Chest pain includes Angina pectoris, Chest discomfort, and Chest pain.

[c] Urinary tract infection includes Urinary tract infection, and Urinary tract infection viral.

[d] Aphasia includes Aphasia, Dysarthria, and Speech disorder.

[e] Ataxia includes Ataxia, Balance disorder, and Gait disturbance.

[f] Paresis includes Facial paralysis, and Peroneal nerve palsy.

[g] Delirium includes Agitation, Hallucination, Irritability, Personality change, and Restlessness.

[h] Depression includes Depression, and Flat affect.

[i] Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, and Renal impairment.

[j] Rash includes Erythema, Rash, Rash maculo-papular, and Rash pustular.

[k] Thrombosis includes Deep vein thrombosis, and Device related thrombosis.

Laboratory Abnormalities

Table 4 presents the most common Grade 3 or 4 laboratory abnormalities based on laboratory data, occurring in at least 10% of patients.

Table 4: Grade 3 or 4 laboratory abnormalities in at least 10% of patients treated with ciltacabtagene autoleucel in Study CARTITUDE-1 (N=97)

Laboratory Abnormality	Grade 3 or 4 (%)
Lymphopenia	99
Neutropenia	98
White blood cell decreased	98
Anemia	72
Thrombocytopenia	63
Aspartate aminotransferase increased	21

Laboratory abnormalities graded using NCI Common Terminology Criteria for Adverse Events version 5.0. Laboratory abnormalities are sorted by decreasing frequency in the Grade column.

Other clinically important Grade 3 or 4 laboratory abnormalities (based on laboratory data) that occurred in less than 10% of patients treated with ciltacabtagene autoleucel include the following: fibrinogen decreased, hypoalbuminemia, alanine aminotransferase increased, hyponatremia, hypocalcemia, gamma glutamyl transferase increased, alkaline phosphatase increased, hypokalemia, blood bilirubin increased.

6.2 Immunogenicity

The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against the extracellular portion of the anti-BCMA CAR pre-dose, and at multiple timepoints post-infusion. In Study CARTITUDE-1, 19 of 97 (19.6%) patients were positive for anti-product antibodies.

There was no clear evidence that the observed anti-product antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy, or safety.

7 DRUG INTERACTIONS

HIV and the lentivirus used to make CARVYKTI have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid tests (NATs) may yield false-positive results in patients who have received CARVYKTI.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on the use of CARVYKTI in pregnant women. No reproductive and developmental toxicity studies in animals have been conducted with CARVYKTI to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether CARVYKTI has the potential to be transferred to the fetus and cause fetal toxicity. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised that there may be risks to the fetus. Pregnancy after CARVYKTI therapy should be discussed with the treating physician.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of CARVYKTI in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CARVYKTI and any potential adverse effects on the breastfed infant from CARVYKTI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

Contraception

There are insufficient data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI.

In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception and male patients with partners of childbearing potential or whose partners were pregnant were instructed to use a barrier method of contraception, until one year after the patient has received CARVYKTI infusion.

See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

Infertility

There are no data on the effect of CARVYKTI on fertility.

8.4 Pediatric Use

Safety and effectiveness of CARVYKTI in pediatric patients have not been established.

8.5 Geriatric Use

Of the 97 patients in Study CARTITUDE-1 that received ciltacabtagene autoleucel, 28% were 65 to 75 years of age, and 8% were 75 years of age or older. CARTITUDE-1 did not include sufficient numbers of patients aged 65 and older to determine whether the effectiveness differs compared with that of younger patients. In 62 patients less than 65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 19% (12/62) and 6% (4/62) respectively. Of the 35 patients ≥65 years of age, all grade and Grade 3 and higher neurologic toxicities occurred in 37% (13/35) and 20% (7/35) respectively.

11 DESCRIPTION

CARVYKTI® (ciltacabtagene autoleucel) is a BCMA-directed genetically modified autologous T cell immunotherapy. CARVYKTI is prepared from the patient's peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and genetically modified *ex vivo* by transduction with a replication-incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain, which consists of two single-domain antibodies linked to a 4-1BB costimulatory domain and a CD3-zeta signaling domain.

The transduced anti-BCMA CAR T cells are expanded in cell culture, washed, formulated into a suspension and cryopreserved. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag. The product is thawed and then infused back into the patient, where the anti-BCMA CAR T cells can recognize and eliminate BCMA-expressing target cells. *[see Dosage and Administration (2.2), How Supplied/Storage and Handling (16)].*

In addition to T cells, CARVYKTI may contain Natural Killer (NK) cells. The formulation contains 5% dimethyl sulfoxide (DMSO).

CARVYKTI® (ciltacabtagene autoleucel)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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.

12.2 Pharmacodynamics

After a single infusion of ciltacabtagene autoleucel, expansion of CAR-positive T cells coincided with decreases of serum soluble BCMA, serum M-protein, and/or free light chains. Across all patients, levels of IL-6, IL-10, IFN-γ and IL-2 receptor alpha increased post-infusion and peaked at Days 7–14. The serum levels of all cytokines generally returned to baseline levels within 2–3 months post-infusion.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ciltacabtagene autoleucel was assessed in 97 patients with multiple myeloma receiving a single infusion at the median dose of 0.71×10^6 CAR positive viable T cells/kg (range: 0.51×10^6 to 0.95×10^6 cells/kg).

Following a single infusion, ciltacabtagene autoleucel exhibited an initial expansion phase followed by a rapid decline, and then a slower decline. However, high inter-individual variability was observed.

Table 5: Pharmacokinetic parameters of ciltacabtagene autoleucel in patients with multiple myeloma

Parameter	Summary Statistics	N=97
C_{max} (copies/µg genomic DNA)	Median (range), n	47806 (7189 - 115234), 97
t_{max} (day)	Median (range), n	12.7 (8.7 - 329.8), 97
$AUC_{0\text{-}28d}$ (copies* day/µg genomic DNA)	Median (range), n	371569 (58691 - 2024126), 97
$t_{1/2}$ (day)	Median (range), n	15.3 (3.0 - 95.4), 42

After the cell expansion, the persistence phase of ciltacabtagene autoleucel was observed for all patients. At the time of analysis (n=65), the median time for CAR transgene levels in peripheral blood to return to the pre-dose baseline level was approximately 100 days (range: 28 to 365 days) post-infusion.

Detectable ciltacabtagene autoleucel exposures in bone marrow indicate a distribution of ciltacabtagene autoleucel from systemic circulation to bone marrow. Similar to blood transgene levels, bone marrow transgene levels declined over time and exhibited high inter-individual variability.

Some patients required tocilizumab, corticosteroids, and anakinra for the management of CRS. Ciltacabtagene autoleucel continues to expand and persist following administration of tocilizumab, corticosteroids, and anakinra. Ciltacabtagene autoleucel median C_{max} and $AUC_{0\text{-}28d}$ in patients treated with tocilizumab (n=68) for CRS were 168% and 209% of those in patients (n=29) who did not receive tocilizumab for CRS, respectively. The median C_{max} and $AUC_{0\text{-}28d}$ of ciltacabtagene autoleucel in patients who received corticosteroids (n=21) for CRS were 186% and 307% of those in patients who did not receive corticosteroids (n=76) for CRS, respectively. In addition, the median C_{max} and $AUC_{0\text{-}28d}$ of ciltacabtagene autoleucel in patients who received anakinra (n=18) for CRS were 139% and 232% of those in patients who did not receive anakinra (n=79) for CRS, respectively.

Specific Populations

The pharmacokinetics of ciltacabtagene autoleucel (C_{max} and $AUC_{0\text{-}28d}$) were not impacted by age (43 to 78 years), gender, body weight, race, mild hepatic dysfunction [(total bilirubin ≤ upper limit of normal (ULN) and aspartate aminotransferase > ULN) or (ULN < total bilirubin ≤1.5 times ULN)] or aspartate aminotransferase > ULN), or mild renal dysfunction (60 mL/min ≤ creatinine clearance [CRCL] <90 mL/min). Formal renal and hepatic impairment studies of CARVYKTI were not conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No genotoxicity or carcinogenicity studies have been performed with CARVYKTI as they were not indicated. *In vitro* studies with CARVYKTI manufactured from healthy donors and patients with multiple myeloma showed no evidence of cytokine independent growth and no preferential integration near genes associated with oncogenic transformation.

No studies have been conducted to evaluate the effects of CARVYKTI on fertility.

14 CLINICAL STUDIES

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 *[see Adverse Reactions (6.1)].*

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 cytogenetic 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 6). The median time to first response was 1 month (range: 0.9 to 10.7 months).

Table 6: 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.

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).

15 REFERENCES

1 Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019; 25: 625-638.
2 National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0; 2017.

CARVYKTI® (ciltacabtagene autoleucel)

16 HOW SUPPLIED/STORAGE AND HANDLING

CARVYKTI is supplied in one infusion bag containing a frozen suspension of genetically modified autologous T cells in 5% DMSO, either as a:

- 70 mL suspension in an infusion bag and metal cassette (NDC 57894-111-01)
  or
- 30 mL suspension in an infusion bag and metal cassette (NDC 57894-111-02)

Each CARVYKTI infusion bag is individually packed in an aluminum cryo-cassette.

Match the identity of the patient with the patient identifiers on the cassette and infusion bag upon receipt.

Store and transport below -120°C, e.g., in a container for cryogenic storage in the vapor phase of liquid nitrogen.

Store CARVYKTI in the original packaging containing the cassette protecting the infusion bag.

Thaw CARVYKTI prior to infusion *[see Dosage and Administration (2)]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ensure that patients understand the risk of manufacturing failure [18%, (17/97 in the clinical study)]. In case of a manufacturing failure, a second manufacturing of CARVYKTI may be attempted. In addition, while the patient awaits the product, additional anticancer treatment (other than lymphodepletion) may be necessary and may increase the risk of adverse reactions during the pre-infusion period, which could delay or prevent the administration of CARVYKTI.

Advise patients that they will be monitored daily for the first 10 days following the infusion at a REMS-certified healthcare facility, and instruct patients to remain within proximity of a certified healthcare facility for at least 4 weeks following the infusion.

Prior to infusion, advise patients of the following risks and to seek immediate medical attention in the event of the following signs or symptoms:

Cytokine Release Syndrome (CRS)

Signs or symptoms of CRS, including fever, chills, fatigue, headache, tachycardia, hypotension, hypoxia, dizziness/lightheadedness or organ toxicities *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*.

Neurologic Toxicities

Signs or symptoms associated with neurologic events, some of which occur days, weeks or months following the infusion including *[see Warnings and Precautions (5.2), Adverse Reactions (6.1)]*:

ICANS: e.g., aphasia, encephalopathy, depressed level of consciousness, seizures, delirium, dysgraphia
Parkinsonism: e.g., tremor, micrographia, bradykinesia, rigidity, shuffling gait, stooped posture, masked facies, apathy, flat affect, lethargy, somnolence
Guillain Barré Syndrome: e.g., motor weakness and polyradiculoneuritis
Peripheral neuropathy: e.g., peripheral motor and/or sensory nerve dysfunction
Cranial Nerve Palsies: e.g., facial paralysis, facial numbness

Prolonged and Recurrent Cytopenias

Signs or symptoms associated with bone marrow suppression including neutropenia, thrombocytopenia, anemia, or febrile neutropenia for several weeks or months. Signs or symptoms associated with bone marrow suppression may recur *[see Warnings and Precautions (5.5), Adverse Reactions (6.1)]*.

Infections

Signs or symptoms associated with infection *[see Warnings and Precautions (5.6), Adverse Reactions (6.1)]*.

Hypersensitivity Reactions

Signs or symptoms associated with hypersensitivity reactions including flushing, chest tightness, tachycardia, and difficulty breathing *[see Warnings and Precautions (5.8)]*.

Advise patients of the need to:

- Have periodic monitoring of blood counts before and after CARVYKTI infusion *[see Warnings and Precautions (5.5)]*.
- Contact Janssen Biotech, Inc. at 1-800-526-7736 if they are diagnosed with a secondary malignancy *[see Warnings and Precautions (5.9)]*.
- Refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after treatment and in the event of any new onset of neurologic toxicities *[see Warnings and Precautions (5.10)]*.
- Tell their physician about their treatment with CARVYKTI before receiving a live virus vaccine *[see Warnings and Precautions (5.7)]*.

Manufactured/Marketed by:
Janssen Biotech, Inc.,
Horsham, PA 19044, USA
U.S. License Number 1864

Marketed by:
Legend Biotech
Somerset, NJ 08873, USA

MEDICATION GUIDE
CARVYKTI® (car-vick-tee)
(ciltacabtagene autoleucel)

Read this Medication Guide before you start your CARVYKTI treatment. The more you know about your treatment, the more active you can be in your care. Talk with your healthcare provider if you have questions about your health condition or treatment. Reading this Medication Guide does not take the place of talking with your healthcare provider about your treatment.

What is the most important information I should know about CARVYKTI?

CARVYKTI may cause side effects that are severe or life-threatening and can lead to death. Call your healthcare provider or get emergency help right away if you get any of the following:

- fever (100.4°F/38°C or higher)
- chills or shaking chills
- fast or irregular heartbeat
- difficulty breathing
- very low blood pressure
- dizziness/light headedness
- effects on your nervous system, some of which can occur days or weeks after you receive the infusion, and may initially be subtle such as:
  - feeling confused, less alert, or disoriented, having difficulty speaking or slurred speech, having difficulty reading, writing, and understanding words, memory loss
  - loss of coordination affecting movement and balance, slower movements, changes in handwriting
  - personality changes including a reduced ability to express emotions, being less talkative, disinterest in activities, and reduced facial expression
  - tingling, numbness, and pain of hands and feet, difficulty walking, leg and/or arm weakness, and difficulty breathing
  - facial numbness, difficulty moving muscles of face and eyes

It is important that you tell your healthcare providers that you have received CARVYKTI and to show them your CARVYKTI Patient Wallet Card. Your healthcare providers may give you other medicines to treat your side effects.

What is CARVYKTI?

- CARVYKTI is a treatment used for adult patients who have cancer of the bone marrow called multiple myeloma. It is used when at least four other kinds of treatment have not worked or have stopped working.
- CARVYKTI is a medicine made from your own white blood cells, which have been changed (genetically modified) to recognize and attack your multiple myeloma cells.

Before you receive CARVYKTI tell your healthcare provider about all your medical conditions, including if you have:

- Current or past neurologic problems (such as seizures, stroke, new or worsening memory loss)
- Lung or breathing problems
- Heart problems
- Liver problems
- Kidney problems
- A recent or active infection
- Low blood counts

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive CARVYKTI?

- CARVYKTI is made from your own white blood cells, so your blood will be collected by a process called 'leukapheresis' (loo-kah-fur-ee-sis). The procedure can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are sent to a manufacturing center to make CARVYKTI. It takes about 4-5 weeks from the time your cells are received at the manufacturing site and are available to be shipped back to your healthcare provider, but the time may vary.
- While CARVYKTI is being made you may get other medicines to treat the multiple myeloma. This is so that your multiple myeloma does not get worse.

Before you get CARVYKTI, your healthcare provider will give you chemotherapy for 3 days to prepare your body.

30 to 60 minutes before you are given CARVYKTI, you may be given other medicines. These may include:

- medicines for an allergic reaction (anti-histamines)
- medicines for fever (such as acetaminophen)

When your CARVYKTI is ready, your healthcare provider will give CARVYKTI to you through a catheter (tube) placed into your vein (intravenous infusion). Your dose of CARVYKTI will be given in one infusion bag. The infusion usually takes approximately 30-60 minutes.

After getting CARVYKTI, you will be monitored at the certified healthcare facility where you received your treatment for at least 10 days after the infusion.

You should plan to stay close to the location where you received your treatment for at least 4 weeks. Your healthcare provider will check to see that your treatment is working and help you with any side effects that may occur. You may be hospitalized if you develop serious side effects until your side effects are under control and it is safe for you to leave the hospital.

Your healthcare provider will want to do blood tests to follow your progress. It is important that you have your blood tested. If you miss an appointment, call your healthcare provider as soon as possible to reschedule.

What should I avoid after receiving CARVYKTI?

- Do not drive, or operate heavy machinery, or do other activities that could be dangerous if you are not mentally alert, for at least 8 weeks after you get CARVYKTI. This is because the treatment can cause memory and coordination problems, sleepiness, confusion, dizziness, seizures, or other neurologic side effects as discussed by your healthcare provider.
- You must not be given certain vaccines called live vaccines for some time before and after CARVYKTI treatment. Talk to your healthcare provider if you need to have any vaccinations.
- Do not donate blood, organs, tissues, or cells for transplantation.

What are the possible or reasonably likely side effects of CARVYKTI?

The most common side effects of CARVYKTI include:

- fever (100.4°F/38°C or higher), chills
- dizziness or light-headedness
- headache, muscle or joint pain, feeling very tired
- altered mental state, confusion
- infections
- low levels of antibodies (immunoglobulins) in the blood
- cough, being short of breath
- diarrhea, nausea, decreased appetite, constipation
- fast or irregular heartbeat
- problems with blood clotting

CARVYKTI can cause a very common side effect called cytokine release syndrome or CRS, which can be severe or fatal. Symptoms of CRS include fever, difficulty breathing, dizziness or lightheadedness, nausea, headache, fast heartbeat, low blood pressure, or fatigue. Tell your healthcare provider right away if you develop fever or any of these other symptoms after receiving CARVYKTI.

CARVYKTI can increase the risk of life-threatening infections including COVID 19 that may lead to death. Tell your healthcare provider right away if you develop fever, chills, or any signs or symptoms of an infection.

CARVYKTI can cause various neurologic side effects, some of which may be severe or fatal. Symptoms include but are not limited to confusion, disorientation, loss of consciousness, seizures, difficulty speaking, reading or writing, tremor, slower movements, changes in personality, depression, tingling and numbness of hands and feet, leg and arm weakness, and facial numbness.

CARVYKTI can lower one or more types of your blood cells (red blood cells, white blood cells, or platelets [cells that help blood to clot]), which may make you feel weak or tired or increase your risk of severe infection or bleeding that may lead to death. After treatment, your healthcare provider will test your blood to check for this. Tell your healthcare provider right away if you get a fever, chills, or any signs or symptoms of an infection, are feeling tired, or have bruising or bleeding.

Having CARVYKTI in your blood may cause some commercial Human Immunodeficiency Virus (HIV) tests to incorrectly give you an HIV-positive result even though you may be HIV-negative.

These are not all the possible side effects of CARVYKTI. Call your healthcare provider if you have any side effects.

You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of CARVYKTI

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. If you would like more information about CARVYKTI, talk with your healthcare provider. You can ask your healthcare provider for information about CARVYKTI that is written for health professionals. For more information go to www.CARVYKTI.com or call 1-800-526-7736.

What are the ingredients in CARVYKTI?

Active ingredient: ciltacabtagene autoleucel

Inactive ingredients: DMSO

Manufactured/Marketed by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License Number 1864
Marketed by: Legend Biotech, Somerset, NJ 08873, USA. For more information, call 1-800-526-7736 or go to www.CARVYKTI.com.

This Medication guide has been approved by the U.S. Food and Drug Administration.

Revised: FEB 2023

cp-258859v6