CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

CARVYKTI® Administration Summary Guide

Preparation through post-infusion monitoring

INDICATIONS AND USAGE

CARVYKTI® (ciltacabtagene autoleucel) 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, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

IMPORTANT SAFETY INFORMATION

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

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.

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.

Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI®.

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.

Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI®.

Immune Effector Cell-associated Enterocolitis (IEC-EC), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI®.

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI®. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®.

Please click here to read full Important Safety Information and click here to read full Prescribing Information, including Boxed Warning, for CARVYKTI®.

Menu

CARVYKTI® treatment process 3

Preparing the patient for their infusion of CARVYKTI® 4

Preparing the infusion 7

Administering CARVYKTI® 12

Considerations for monitoring 13

CARVYKTI® Important Safety Information 14

Summary 19

SELECTED IMPORTANT SAFETY INFORMATION

Fatal or life-threatening reactions occurred in patients following treatment with CARVYKTI®, including Cytokine Release Syndrome (CRS), Parkinsonism, and Guillain-Barré syndrome, and their associated complications, and Hemophagocytic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS). HLH/MAS can occur with CRS or neurologic toxicities. Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS), which can be fatal or life-threatening, occurred after treatment, before CRS onset, concurrently with CRS, after CRS resolution, or in absence of CRS. A numerically higher percent of early mortality was observed as compared to the control arm in CARTITUDE-4. Immune Effector Cell-associated Enterocolitis (IEC-EC), including fatal or life-threatening reactions, occurred following treatment. Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery, and secondary hematological malignancies, including myelodysplastic syndrome, acute myeloid leukemia, and T-cell malignancies occurred following treatment.

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CARVYKTI® treatment process [1-3]

1	**LEUKAPHERESIS** [1,2]	• Patient's white blood cells are extracted over the course of approximately **3 to 6 hours**. The immune cells are then cryopreserved and sent to the manufacturing site. Leukapheresis is likely to be performed at the CARVYKTI® Activated Treatment Center
2	**BRIDGING THERAPY** [1]	• Patients **may receive additional therapy** for disease control before their treatment with CARVYKTI® at the discretion of the Activated Treatment Center physician, who may consult with the primary oncologist
3	**MANUFACTURING** [1]	• T cells are isolated and **genetically modified** to express the CARVYKTI® CAR. After quality control release, the CARVYKTI® CAR-T cells are cryopreserved and returned to the CARVYKTI® Activated Treatment Center for infusion
4	**LYMPHODEPLETION** [1]	• Patients are lymphodepleted with cyclophosphamide + fludarabine **daily for 3 days** (completed 2 to 4 days prior to infusion of CARVYKTI®)
5	**INFUSION** [1]	• CARVYKTI® is administered in a **single infusion that takes approximately 30 to 60 minutes** at a CARVYKTI® Activated Treatment Center. Patients should remain within proximity of the CARVYKTI® Activated Treatment Center for at least 2 weeks following infusion **CARVYKTI® dose is 0.5-1.0×10^6 CAR+ viable T cells per kg body weight, with a maximum dose of 1×10^8 CAR+ viable T cells per one-time infusion.** **Delay the infusion of CARVYKTI® if your patient encounters:** • 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
6	**MONITORING** [1,3]	• Patients are monitored periodically for the first 2 weeks after CARVYKTI® infusion, including daily at the CARVYKTI® Activated Treatment Center for the **first 7 days following CARVYKTI® infusion** • **Patients are monitored long-term** by their primary oncology care team in collaboration with the CARVYKTI® Activated Treatment Center team

Inform patients of the risk of early mortality. In a clinical study, treatment in the CARVYKTI® arm was associated with a higher rate of death (14%) compared to the control arm (12%) in the first 10 months from randomization. This higher rate of death was observed before receiving CARVYKTI® and after treatment with CARVYKTI®. The reasons for death were progression of multiple myeloma and adverse events.

CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor-T cell.

References: 1. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Beaupierre A, Lundberg R, Marrero L, et al. Management across settings: an ambulatory and community perspective for patients undergoing CAR T-cell therapy in multiple care settings. *Clin J Oncol Nurs*. 2019;23(2):27-34. **3.** Beaupierre A, Kahle N, Lundberg R, et al. Educating multidisciplinary care teams, patients, and caregivers on CAR T-cell therapy. *J Adv Pract Oncol*. 2019;10(Suppl 3):29-40.

SELECTED IMPORTANT SAFETY INFORMATION

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Preparing the patient for their infusion of CARVYKTI®

STEP 1: LEUKAPHERESIS[1,2]

Leukapheresis occurs **after consultation**, **patient eligibility is confirmed**, **and CARVYKTI® is prescribed**. Understanding this critical step can help you better prepare your patient for future treatment.

- **Collection of the patient's white blood cells** will likely take place under supervision of the **CARVYKTI® Activated Treatment Center**. The process may take 3 to 6 hours
- Harvested cells will be cryopreserved and are provided to the manufacturing facility for genetic modification and *in vitro* expansion

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Preparing the patient for their infusion of CARVYKTI® (cont)

STEP 2: BRIDGING THERAPY (IF PRESCRIBED)[1,2]

While manufacturing of CAR-T cells is underway, bridging therapy is often used in certain circumstances for disease control or reduction in tumor burden, including:

- For patients with high tumor burden
- For patients with aggressive disease
- To reduce baseline burden of disease

Bridging therapies may vary between patients, who should be monitored for any adverse reactions.

CAR-T=chimeric antigen receptor-T cell.

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Preparing the patient for their infusion of CARVYKTI® (cont)

STEP 3: MANUFACTURING

Once the patient's cryopreserved cells are sent to the manufacturing facility, there is a waiting period that varies in length.

During manufacturing, the patient's T cells are reprogrammed to express a chimeric antigen receptor (CAR) that identifies and eliminates cells that have B cell maturation antigen (BCMA) receptors.

- The patient's T cells are isolated, and then genetically modified to express the CARVYKTI® CAR
- CARVYKTI® CAR-T cells are cryopreserved and returned to the CARVYKTI® Activated Treatment Center for infusion. The product must pass a sterility test before release for shipping as a frozen suspension in a patient-specific infusion bag

CAR=chimeric antigen receptor; CAR-T=chimeric antigen receptor-T cell.

Reference: CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

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Preparing the infusion

Ensure personnel involved in product handling, storage, and infusion have been trained according to your institution's practices. Please refer to the *CARVYKTI® (ciltacabtagene autoleucel) Product Handling Guide* (cp-272168) for more details.

STEP 4: LYMPHODEPLETION

- Two to 4 days before infusion of CARVYKTI®, patients will have completed a lymphodepleting chemotherapy regimen at the CARVYKTI® Activated Treatment Center
  - The standard regimen is cyclophosphamide 300 mg/m^2 plus fludarabine 30 mg/m^2 administered intravenously **daily for 3 days**
- 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

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Preparing the infusion (cont)

Receipt of CARVYKTI®

CARVYKTI® is provided in a patient-specific infusion bag, either 30 mL or 70 mL, as a frozen suspension of genetically modified autologous T cells.

1. All sites approved for infusion will support required storage conditions for vapor phase of liquid nitrogen
2. 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
3. Confirm the patient's identity with the patient identifiers on the shipper
4. 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

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Preparing the infusion (cont)

Clinical assessment before infusion and premedication

Clinical assessment

Prior to thawing CARVYKTI®, ensure that a minimum of 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period. 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 to 60 minutes prior to CARVYKTI® infusion:

- Antipyretic (oral or IV acetaminophen 650 mg to 1000 mg)
- Antihistamine (oral or IV diphenhydramine 25 mg to 50 mg, or equivalent)
- **Avoid the use of prophylactic systemic corticosteroids**, as they may interfere with the activity of CARVYKTI®

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Preparing the infusion (cont)

STEP 5: PREPARATION OF CARVYKTI® FOR INFUSION

Check each box as you complete the corresponding step for infusion preparation to help identify which details come next

- **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
- **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®** product 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
- Once patient identification is confirmed, **remove the CARVYKTI®** product bag from the cassette
- **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**

Continued on next page

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Preparing the infusion (cont)

STEP 5: PREPARATION OF CARVYKTI® FOR INFUSION (cont)

Here are the steps you must complete for proper infusion preparation

- **Place** the infusion bag **inside a sealable plastic bag** (preferably sterile) prior to thawing
- **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**
- 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
- Once thawed, the CARVYKTI® infusion **must be administered and completed within 2.5 hours** at room/ambient temperature (20°C to 25°C)
- **Do not refreeze or refrigerate thawed product**

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Administering CARVYKTI®

- For autologous infusion only
- Central venous access may be utilized for the infusion of CARVYKTI® and is encouraged in patients with poor peripheral access
- A CARVYKTI® dose is 0.5-1.0 × 10^6 CAR+ viable T cells per kg body weight, with a maximum dose of 1 × 10^8 CAR+ viable T cells per one-time infusion

Administration process

Ensure that a minimum of 2 doses of tocilizumab and emergency equipment are available prior to infusion and during the recovery period

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

Prime the tubing of the infusion set with normal saline prior to infusion

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. **Do NOT use a leukocyte-depleting filter**

Gently mix the contents of the bag during CARVYKTI® infusion to disperse cell clumps

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.

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Considerations for monitoring

STEP 6: MONITORING

During the infusion[1,2]

The CARVYKTI® infusion usually takes **approximately 30-60 minutes**. During the infusion, monitor patients according to the center's policy for:

- Oxygen saturation
- Pulse rate
- Blood pressure
- Respiratory changes
- Other symptoms such as itchy skin, shortness of breath, difficulty breathing, etc

After the infusion[1]

- Patients are monitored periodically for the first 2 weeks after CARVYKTI® infusion, including daily at the CARVYKTI® Activated Treatment Center for the **first 7 days following CARVYKTI® infusion**
- **Patients are monitored long-term** by their primary oncology care team in collaboration with the CARVYKTI® Activated Treatment Center team for at least 4 weeks post-infusion. Some side effects may continue to present and/or occur 4 weeks or more after CARVYKTI® infusion

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 2 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.

Report suspected adverse reactions

Janssen Biotech, Inc.: 1-800-JANSSEN (1-800-526-7736) **FDA:** 1-800-FDA-1088 (1-800-332-1088) fda.gov/medwatch

References: 1. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Zhang X, Sun D, Jiang G-C. Relevant nursing measures for the adverse reactions associated with chimeric antigen receptor-T cells (CAR-T) immunotherapy: a systematic review of case reports. *Front Nurs*. 2019;6(2):87-96.

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Important Safety Information

INDICATIONS AND USAGE

CARVYKTI® (ciltacabtagene autoleucel) 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, who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

IMPORTANT SAFETY INFORMATION

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

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.

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.

Parkinsonism and Guillain-Barré syndrome (GBS) and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI®.

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.

Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI®.

Immune Effector Cell-associated Enterocolitis (IEC-EC), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI®.

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred in patients following treatment with CARVYKTI®. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®.

WARNINGS AND PRECAUTIONS

Increased early mortality. In CARTITUDE-4, a (1:1) randomized controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI® treatment arm compared to the control arm. Among patients with deaths occurring within the first 10 months from randomization, a greater proportion (29/208; 14%) occurred in the CARVYKTI® arm compared to (25/211; 12%) in the control arm. Of the 29 deaths that occurred in the CARVYKTI® arm within the first 10 months of randomization, 10 deaths occurred prior to CARVYKTI® infusion, and 19 deaths occurred after CARVYKTI® infusion. Of the 10 deaths that occurred prior to CARVYKTI® infusion, all occurred due to disease progression, and none occurred due to adverse events. Of the 19 deaths that occurred after CARVYKTI® infusion, 3 occurred due to disease progression, and 16 occurred due to adverse events. The most common adverse events were due to infection (n=12).

Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® for RRMM in the CARTITUDE-1 & -4 studies (N=285), CRS occurred in 84% (238/285), including ≥ Grade 3 CRS (ASTCT 2019) in 4% (11/285) of patients. Median time to onset of CRS, any grade, was 7 days (range: 1 to 23 days). CRS resolved in 82% with a median duration of 4 days (range: 1 to 97 days). The most common manifestations of CRS in all patients combined (≥10%) included fever (84%), hypotension (29%) and aspartate aminotransferase increased (11%). Serious events that may be associated with CRS include pyrexia, hemophagocytic lymphohistiocytosis, respiratory failure, disseminated

Continued on next page

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Important Safety Information (cont)

WARNINGS AND PRECAUTIONS (cont)

intravascular coagulation, capillary leak syndrome, and supraventricular and ventricular tachycardia. CRS occurred in 78% of patients in CARTITUDE-4 (3% Grade 3 to 4) and in 95% of patients in CARTITUDE-1 (4% Grade 3 to 4).

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.

Confirm that a minimum of 2 doses of tocilizumab are available prior to infusion of CARVYKTI®.

Of the 285 patients who received CARVYKTI® in clinical trials, 53% (150/285) patients received tocilizumab; 35% (100/285) received a single dose, while 18% (50/285) received more than 1 dose of tocilizumab. Overall, 14% (39/285) of patients received at least 1 dose of corticosteroids for treatment of CRS.

Monitor patients at least daily for 7 days following CARVYKTI® infusion for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 2 weeks after infusion. At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids.

Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

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, GBS, 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.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & 4 studies for RRMM, one or more neurologic toxicities occurred in 24% (69/285), including ≥ Grade 3 cases in 7% (19/285) of patients. Median time to onset was 10 days (range: 1 to 101) with 63/69 (91%) of cases developing by 30 days. Neurologic toxicities resolved in 72% (50/69) of patients with a median duration to resolution of 23 days (range: 1 to 544). Of patients developing neurotoxicity, 96% (66/69) also developed CRS. Subtypes of neurologic toxicities included ICANS in 13%, peripheral neuropathy in 7%, cranial nerve palsy in 7%, parkinsonism in 3%, and immune mediated myelitis in 0.4% of the patients.

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.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, ICANS occurred in 13% (36/285), including Grade ≥3 in 2% (6/285) of the patients. Median time to onset of ICANS was 8 days (range: 1 to 28 days). ICANS resolved in 30 of 36 (83%) of patients, with a median time to resolution of 3 days (range: 1 to 143 days). Median duration of ICANS was 6 days (range: 1 to 1229 days) in all patients, including those with ongoing neurologic events at the time of death or data cutoff. Of patients with ICANS, 97% (35/36) had CRS. The onset of ICANS occurred during CRS in 69% of patients, before and after the onset of CRS in 14% of patients, respectively.

Immune Effector Cell-associated Neurotoxicity Syndrome occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3) and in 23% of patients in CARTITUDE-1 (3% Grade 3). The most frequent (≥2%) manifestations of ICANS included encephalopathy (12%), aphasia (4%), headache (3%), motor dysfunction (3%), ataxia (2%), and sleep disorder (2%).

Monitor patients at least daily for 7 days following CARVYKTI® infusion for signs and symptoms of ICANS. Rule out other causes of ICANS symptoms. Monitor patients for signs or symptoms of ICANS for at least 2 weeks after infusion and treat promptly. Neurologic toxicity should be managed with supportive care and/or corticosteroids as needed. Advise patients to avoid driving for at least 2 weeks following infusion.

Parkinsonism: Neurologic toxicity with parkinsonism has been reported in clinical trials of CARVYKTI®. Among patients receiving

Continued on next page

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Important Safety Information (cont)

WARNINGS AND PRECAUTIONS (cont)

CARVYKTI® in the CARTITUDE-1 & -4 studies, parkinsonism occurred in 3% (8/285), including Grade ≥3 in 2% (5/285) of the patients. Median time to onset of parkinsonism was 56 days (range: 14 to 914 days). Parkinsonism resolved in 1 of 8 (13%) of patients with a median time to resolution of 523 days. Median duration of parkinsonism was 243.5 days (range: 62 to 720 days) in all patients, including those with ongoing neurologic events at the time of death or data cutoff. The onset of parkinsonism occurred after CRS for all patients and after ICANS for 6 patients.

Parkinsonism occurred in 1% of patients in CARTITUDE-4 (no Grade 3 to 4) and in 6% of patients in CARTITUDE-1 (4% Grade 3 to 4).

Manifestations of parkinsonism included movement disorders, cognitive impairment, and personality changes. 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 GBS occurred following treatment with CARVYKTI® 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 occurred 25 days following treatment with CARVYKTI® in CARTITUDE-4 in a patient who received CARVYKTI® as subsequent therapy. 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 occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, peripheral neuropathy occurred in 7% (21/285), including Grade ≥3 in 1% (3/285) of the patients. Median time to onset of peripheral neuropathy was 57 days (range: 1 to 914 days). Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1 to 215 days). Median duration of peripheral neuropathy was 149.5 days (range: 1 to 692 days) in all patients including those with ongoing neurologic events at the time of death or data cutoff.

Peripheral neuropathies occurred in 7% of patients in CARTITUDE-4 (0.5% Grade 3 to 4) and in 7% of patients in CARTITUDE-1 (2% Grade 3 to 4). Monitor patients for signs and symptoms of peripheral neuropathies. Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS.

Cranial nerve palsies occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, cranial nerve palsies occurred in 7% (19/285), including Grade ≥3 in 1% (1/285) of the patients. Median time to onset of cranial nerve palsies was 21 days (range: 17 to 101 days). Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1 to 209 days). Median duration of cranial nerve palsies was 70 days (range: 1 to 262 days) in all patients, including those with ongoing neurologic events at the time of death or data cutoff. Cranial nerve palsies occurred in 9% of patients in CARTITUDE-4 (1% Grade 3 to 4) and in 3% of patients in CARTITUDE-1 (1% Grade 3 to 4).

The most frequent cranial nerve affected was the 7th cranial nerve. Additionally, cranial nerves III, V, and VI have been reported to be affected.

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.

Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS): Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, HLH/MAS occurred in 1% (3/285) of patients. All events of HLH/MAS had onset within 99 days of receiving CARVYKTI®, with a median onset of 10 days (range: 8 to 99 days), and all occurred in the setting of ongoing or worsening CRS. The manifestations of HLH/MAS included hyperferritinemia, hypotension, hypoxia with diffuse alveolar damage, coagulopathy and hemorrhage, cytopenia, and multi-organ dysfunction, including renal dysfunction and respiratory failure.

Continued on next page

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Important Safety Information (cont)

WARNINGS AND PRECAUTIONS (cont)

Patients who develop HLH/MAS have an increased risk of severe bleeding. Monitor hematologic parameters in patients with HLH/MAS and transfuse per institutional guidelines. Fatal cases of HLH/MAS occurred following treatment with CARVYKTI®.

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.

Prolonged and Recurrent Cytopenias: Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI® infusion.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, Grade 3 or higher cytopenias not resolved by Day 30 following CARVYKTI® infusion occurred in 62% (176/285) of the patients and included thrombocytopenia 33% (94/285), neutropenia 27% (76/285), lymphopenia 24% (67/285), and anemia 2% (6/285). After Day 60 following CARVYKTI® infusion, 22%, 20%, 5%, and 6% of patients had a recurrence of Grade 3 or 4 lymphopenia, neutropenia, thrombocytopenia, and anemia, respectively, after initial recovery of their Grade 3 or 4 cytopenia. Seventy-seven percent (219/285) 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. Sixteen and 25 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.

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.

Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, infections occurred in 57% (163/285), including Grade ≥3 in 24% (69/285) of patients. Grade 3 or 4 infections with an unspecified pathogen occurred in 12%, viral infections in 6%, bacterial infections in 5%, and fungal infections in 1% of patients. Overall, 5% (13/285) of patients had Grade 5 infections, 2.5% of which were due to COVID-19. Patients treated with CARVYKTI® had an increased rate of fatal COVID-19 infections compared to the standard therapy arm.

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 5% of patients after CARVYKTI® 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. 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.

Reactivation of John Cunningham (JC) virus, leading to progressive multifocal leukoencephalopathy (PML), including cases with fatal outcomes, have been reported following treatment. Perform appropriate diagnostic evaluations in patients with neurological adverse events.

Hypogammaglobulinemia can occur in patients receiving treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, hypogammaglobulinemia adverse event was reported in 36% (102/285) of patients; laboratory IgG levels fell below 500 mg/dL after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500 mg/dL after infusion occurred in 94% (267/285) of patients treated. Fifty-six percent (161/285) of

Continued on next page

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Important Safety Information (cont)

WARNINGS AND PRECAUTIONS (cont)

patients received intravenous immunoglobulin (IVIG) post CARVYKTI® 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®.

Hypersensitivity Reactions occurred following treatment with CARVYKTI®. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, hypersensitivity reactions occurred in 5% (13/285), all of which were ≤2 Grade. Manifestations of hypersensitivity reactions included flushing, chest discomfort, tachycardia, wheezing, tremor, burning sensation, non-cardiac chest pain, and pyrexia.

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.

Immune effector cell-associated enterocolitis (IEC-EC) has occurred in patients treated with CARVYKTI®. Manifestations include severe or prolonged diarrhea, abdominal pain, and weight loss requiring parenteral nutrition. IEC-EC has been associated with fatal outcome from perforation or sepsis. Manage according to institutional guidelines, including referral to gastroenterology and infectious disease specialists.

In cases of refractory IEC-EC, consider additional workup to exclude alternative etiologies, including T-cell lymphoma of the GI tract, which has been reported in the post marketing setting.

Secondary Malignancies: Patients treated with CARVYKTI® may develop secondary malignancies. Among patients receiving CARVYKTI® in the CARTITUDE-1 & -4 studies, myeloid neoplasms occurred in 5% (13/285) of patients (9 cases of myelodysplastic syndrome, 3 cases of acute myeloid leukemia, and 1 case of myelodysplastic syndrome followed by acute myeloid leukemia). The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI®. Ten of these 13 patients died following the development of myeloid neoplasms; 2 of the 13 cases of myeloid neoplasm occurred after initiation of subsequent antimyeloma therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting. T-cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T-cell immunotherapies, including CARVYKTI®. Mature T-cell malignancies, including CAR-positive tumors, may present as soon as weeks following infusions, and may include fatal outcomes.

Monitor lifelong 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.

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 Grade 3 or 4 laboratory adverse reactions (incidence greater than or equal to 50%) include lymphopenia, neutropenia, white blood cell decreased, thrombocytopenia, and anemia.

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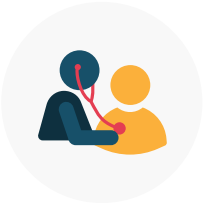
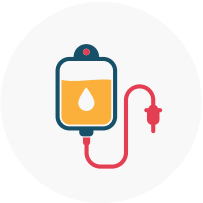
Support your patients treated with CARVYKTI®



Educate your patients on the treatment experience with CARVYKTI® (ciltacabtagene autoleucel)



Know the details of infusion preparation and administration

Learn more about CARVYKTI® at

CARVYKTIHCP.COM

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Johnson&Johnson

LEGEND BIOTECH

CARVYKTI® (ciltacabtagene autoleucel) Suspension for IV Infusion