CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

CARVYKTI® (ciltacabtagene autoleucel)

Product Handling Guide

This material is designed to help you follow the steps for receipt, storage, handling, thawing, preparation, and administration of CARVYKTI®.

If some of the processes described in this document are performed by other departments or personnel, please share this document accordingly.

Ensure personnel involved in product handling, storage, and infusion steps have been trained according to the institution's practices.

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®.

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®.

CARVYKTI® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI® REMS Program.

Please read Important Safety Information on pages 10-14 and full Prescribing Information, including Boxed Warning, for CARVYKTI®.

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SELECTED IMPORTANT SAFETY INFORMATION

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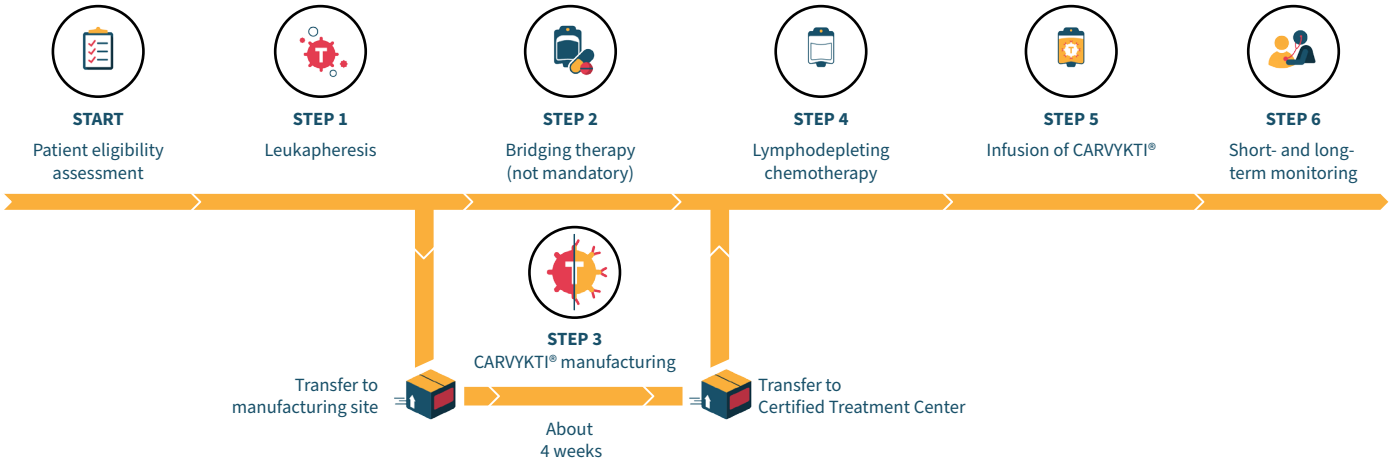
Introduction to CARVYKTI®[1]

- 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. BCMA is primarily expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. 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
- 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

The CARVYKTI® Cell Therapy Process

THERE ARE MULTIPLE STEPS INVOLVED IN CAR-T THERAPY



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BCMA=B cell maturation antigen; CAR-T=chimeric antigen receptor-T cell.

Reference: 1. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

The CARVYKTI® Process[1]

LEUKAPHERESIS

Leukapheresis involves removing the patient's T cells, after which they will be packaged, cryopreserved, and sent to the CAR-T cell manufacturing facility. Leukapheresis can take 3 to 6 hours and may need to be repeated.

BRIDGING THERAPY

In the pivotal CARTITUDE-1 trial, most patients (75%) treated with ciltacabtagene autoleucel received bridging therapy for control of their multiple myeloma during the manufacturing process. In CARTITUDE-4, patients with relapsed and lenalidomide-refractory multiple myeloma, who received at least 1 prior line of treatment, were randomized 1:1 to receive either a sequence of apheresis, bridging therapy, lymphodepletion, and CARVYKTI® (n=208), or standard therapy which included daratumumab, pomalidomide and dexamethasone (DPd) or bortezomib, pomalidomide and dexamethasone (PVd). Patients randomized to CARVYKTI® received at least one cycle of DPd or PVd bridging therapy for disease control between leukapheresis and the start of the lymphodepleting chemotherapy. Bridging therapy may take place at a Certified Treatment Center or the patient's local oncology practice.

Preparing the Patient for CARVYKTI® Infusion[1]

LYMPHODEPLETING CHEMOTHERAPY

- Confirm the availability of CARVYKTI® prior to starting the lymphodepleting regimen
- Administer the lymphodepleting regimen of cyclophosphamide 300 mg/m^2 intravenously daily and fludarabine 30 mg/m^2 intravenously daily for 3 days. For dose adjustments in renal impairment, see corresponding manufacturer's prescribing information
- 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 patients with prior allogenic 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

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Before Administration[1]

CLINICAL ASSESSMENT PRIOR TO CARVYKTI® INFUSION

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:
  - Antipyretics (oral or intravenous acetaminophen 650 to 1,000 mg)
  - Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent)
- Avoid use of prophylactic systemic corticosteroids as their use may interfere with the activity of CARVYKTI®

Dosage and Administration[1]

CARVYKTI® DOSE

- CARVYKTI® is for autologous and intravenous use only
- CARVYKTI® is provided as a single infusion that takes approximately 30 to 60 minutes containing a suspension of chimeric antigen receptor (CAR)+ viable T cells in one infusion bag. The dose is 0.5-1.0×10^6 CAR+ viable T cells per kg of body weight, with a maximum dose of 1×10^8 CAR+ viable T cells per single infusion

SELECTED IMPORTANT SAFETY INFORMATION

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Receipt of CARVYKTI®[1]

- 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

Please consult the Cilta-cel CAR-T Receipt & Storage Manual for the specific guidance for receipt and storage requirements for CARVYKTI® as well as training provided to your site.[3]

Storage of CARVYKTI®

- The product must be stored and transported according to the conditions on the label, below -120°C, in a container for cryogenic storage in the vapor phase of LN2[1]
- Handling of the product outside of the cryogenic storage (-120°C) will cause a very rapid rise in temperature and should be minimized/avoided[2]
- Store in the original packaging containing the cassette protecting the infusion bag[1]
- Temperature conditions during on-site storage of CARVYKTI® must be monitored, verified, and recorded on a temperature log or temperature alarm log daily, during site working days[3]
- If a temperature out-of-range event happens at any time during storage, immediately quarantine the product according to the manufacturing requirements (eg, LN2), and contact the local Janssen representative at 1-800-526-7736[3]

Handling and Disposal of CARVYKTI®[1]

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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LN2=liquid nitrogen.

References: 1. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Data on file. **3.** Data on file. Cilta-cel CAR-T Receipt and Storage Manual.

Preparation of CARVYKTI® for Infusion[1]

- 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® infusion 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 infusion bag for any breaches of container integrity such as breaks or cracks before and after thawing. Do not administer if the bag is compromised; 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, and/or resuspend CARVYKTI® in new media prior to infusion
7. Do not re-freeze or refrigerate thawed product

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Administration of CARVYKTI® [1-4]

- 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

- A non-leukocyte depleting filter is commonly referred to as a blood filter. All blood and cell products must be administered through a filter in order to remove cell clots and thrombi. Standard blood filters, with a pore size of 170–260 µm, trap large aggregates and clots
- CARVYKTI® is an engineered T cell product derived from a patient's blood and therefore has been developed to follow standard practices of administration as a blood and cell product. To ensure the engineered T cells are not filtered out during infusion, while preventing potential agglomerates and clots of material from being infused to the patient, a non-leukocyte depleting filter (blood filter) must be used. If agglomerates/thrombi enter the bloodstream, there is a potential for the formation of clots, which can lead to pulmonary embolism
- Blood filters are also available as microagglomerate filters which have a pore size range of 10–40 µm. CARVYKTI® has not been evaluated for administration with microagglomerate filters and therefore they must NOT be used during infusion

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Monitoring After Infusion[1]

- Administer CARVYKTI® at a REMS-Certified Treatment Center
- Monitor patients at least daily for 10 days following CARVYKTI® infusion at a Certified Treatment Center 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 the Certified Treatment Center for at least 4 weeks following infusion
- Instruct patients to refrain from driving or hazardous activities for at least 8 weeks following infusion

Accidental Exposure

Accidental exposure to CARVYKTI® must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with CARVYKTI® must be decontaminated with appropriate disinfectant.

COVID-19[1]

Patients treated with ciltacabtagene autoleucel have an increased risk of fatal COVID-19 infections. Follow institutional guidelines for the vaccination and management of immunocompromised patients with COVID-19.

Reporting of Adverse Reactions

Any adverse reactions and/or quality complaints should be reported.

- In order to improve the traceability of CARVYKTI® the batch/lot number of the administered product should be clearly recorded when reporting an adverse reaction
- When reporting a suspected adverse reaction, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment date

Report suspected adverse reactions[1]

Janssen Biotech, Inc.: 1-800-JANSSEN (1-800-526-7736)
FDA: 1-800-FDA-1088 (1-800-332-1988)
fda.gov/medwatch

CARVYKTI® is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called CARVYKTI® REMS[1]

CALL 1-844-672-0067 (Monday-Friday, 8 AM-8 PM ET) VISIT CARVYKTIREMS.COM

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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 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.

Ensure that a minimum of two 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 one dose of corticosteroids for treatment of CRS.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS (cont)

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.

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 cut off. 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 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.

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

IMPORTANT SAFETY INFORMATION (cont)

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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 cut off.

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 cut off. 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.

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.

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.

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

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

IMPORTANT SAFETY INFORMATION (cont)

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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.

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 500mg/dl after infusion in 93% (265/285) of patients. Hypogammaglobulinemia either as an adverse reaction or laboratory IgG level below 500mg/dl, after infusion occurred in 94% (267/285) of patients treated. Fifty six percent (161/285) of 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 ≤Grade 2. 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.

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

IMPORTANT SAFETY INFORMATION (cont)

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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 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.

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.

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.

Please read full Prescribing Information, including Boxed Warning, for CARVYKTI®.

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