CARVYKTI®
(ciltacabtagene autoleucel) Suspension for IV Infusion

CARVYKTI® Adverse Reactions Identification and Management Considerations Summary Guide

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®.

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Prior to the patient's CARVYKTI® 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

Counsel patients

Advise patients that they will be monitored daily for the first 7 days following the infusion at a CARVYKTI® Activated Treatment Center, and instruct patients to remain within proximity of an Activated Treatment Center for at least 2 weeks following the infusion.

Consider monitoring patients before, during, and after CARVYKTI® infusion according to the center's policy for[1,2]:

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

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.[1]

References: 1. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. **2.** Zhang X, et al. *Front Nurs.* 2019;6(2):87-95.

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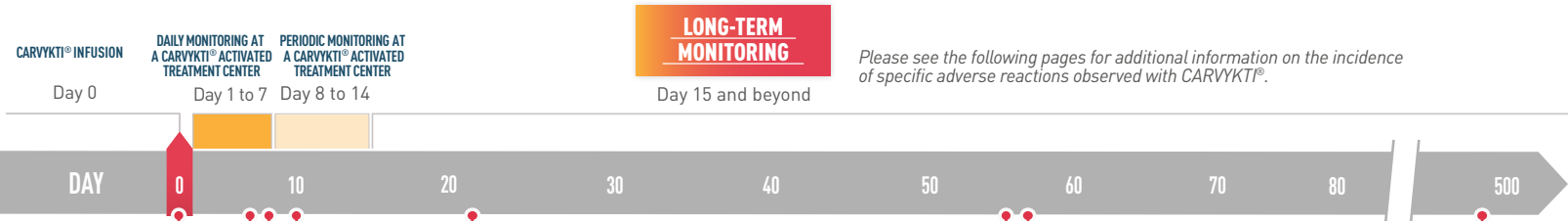
CARVYKTI® infusion and monitoring timeline

The safety data described in this section reflect exposure to CARVYKTI® in 285 patients with relapsed or refractory multiple myeloma: one randomized, open label study with 188 patients in CARTITUDE-4 and one single-arm, open label study with 97 patients in CARTITUDE-1. Because clinical trials are conducted under widely varying conditions, adverse reactions observed in clinical trials may not reflect the rates observed in practice.

Among Patients Receiving CARVYKTI® in the CARTITUDE-4 and CARTITUDE-1 Studies (N=285)[1]



Please see the following pages for additional information on the incidence of specific adverse reactions observed with CARVYKTI®.

HYPERSENSITIVITY REACTIONS

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

CRS

MEDIAN TIME TO ONSET
7 days (range, 1-23 days)

MEDIAN DURATION
4 days (range, 1-97 days)

ICANS

MEDIAN TIME TO ONSET
8 days (range, 1-28 days)

MEDIAN DURATION
6 days (range, 1-1229 days)

HLH/MAS

MEDIAN TIME TO ONSET
10 days (range, 8-99 days)

CRANIAL NERVE PALSIES

MEDIAN TIME TO ONSET
21 days (range, 17-101 days)

MEDIAN DURATION
70 days (range, 1-262 days)

PARKINSONISM

MEDIAN TIME TO ONSET
56 days (range, 14-914)
MEDIAN DURATION
243.5 days (range, 62-720 days)

PERIPHERAL NEUROPATHY

MEDIAN TIME TO ONSET
57 days (range, 1–914 days)

MEDIAN DURATION
149.5 days (range, 1-692 days)

SECONDARY MALIGNANCIES

MEDIAN TIME TO ONSET (MYELOID NEOPLASMS)
447 days (range, 56-870 days)

INCREASED EARLY MORTALITY

Inform patients of the risk of early mortality, which has occurred prior to or after infusion. In CARTITUDE-4, a randomized (1:1), controlled trial, there was a numerically higher percentage of early deaths in patients randomized to the CARVYKTI® treatment arm [29/208; 14%] compared to the control arm [25/211; 12%] within the first 10 months from randomization.

OTHER ADVERSE REACTIONS

Other adverse reactions that may continue to present and/or occur 4 weeks or more after CARVYKTI® infusion include prolonged and/or recurrent cytopenias, Guillain-Barré syndrome (GBS),* immune mediated myelitis, hemophagocytic lymphohistiocytosis/macrophage activation syndrome,† infections/viral reactivation, hypogammaglobulinemia, immune effector cell-associated enterocolitis (IEC-EC), and secondary malignancies. Monitor for these reactions as they can be severe, life-threatening, or fatal.

CRS=cytokine release syndrome; HLH=hemophagocytic lymphohistiocytosis; ICANS=immune effector cell-associated neurotoxicity syndrome; MAS=macrophage activation syndrome.

*A fatal outcome following development of GBS following treatment with CARVYKTI® despite treatment with intravenous immunoglobulin.

†Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

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

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Long-term monitoring for serious adverse reactions

LONG-TERM MONITORING

The following side effects may continue to present and/or occur 4 weeks or more after CARVYKTI® infusion:

- Cytokine release syndrome
- Neurologic toxicities, including immune effector cell–associated neurotoxicity syndrome
- Parkinsonism
- Guillain-Barré Syndrome
- Immune mediated myelitis
- Peripheral neuropathy
- Cranial nerve palsies
- Hemophagocytic lymphohistiocytosis/Macrophage Activation Syndrome
- Prolonged and/or recurrent cytopenias
- Serious infections, including febrile neutropenia
- Hypogammaglobulinemia
- Immune effector cell-associated enterocolitis (IEC-EC)
- Secondary malignancies

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 following CARVYKTI® infusion. Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery for at least 2 weeks following infusion of CARVYKTI®, and in the event of new onset of any neurologic toxicities.

Educate your patient and their care partner on identifying side effects when they happen and how to report them to healthcare providers on the multidisciplinary team

Continued communication and collaboration is essential for patient transition to long-term monitoring and follow-up, including the importance of care partner support

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

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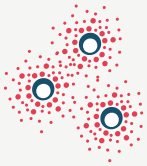
MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Cytokine release syndrome (CRS)



CRS, including fatal or life-threatening reactions, occurred after CARVYKTI® infusion.[1]

In CARTITUDE-4 and CARTITUDE-1 (N=285)

ANY GRADE	GRADE ≥3 (2019 ASTCT Grade)
84% (n=238/285)	**4%** (n=11/285)

In CARTITUDE-4 (N=188)

ANY GRADE	GRADE 3-4
78%	**3%**

In CARTITUDE-1 (N=97)

ANY GRADE	GRADE 3-4
95%	**4%**

- Identify CRS based on clinical presentation. 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 of the USPI
- Ensure that a minimum of 2 doses of tocilizumab are available for each patient prior to CARVYKTI® infusion and are available within 2 hours after CARVYKTI® infusion, if needed, for treatment of CRS
- In patients with early onset fever (if onset is less than 72 hours after infusion), tocilizumab should be considered
- At the first sign of CRS, immediately institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids, depending on CRS grade (See CARVYKTI® USPI)
- Evaluation for hemophagocytic lymphohistiocytosis should be considered in patients with severe or unresponsive CRS
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time
- If CRS is suspected, manage according to the recommendations in Table 1 of section 2.3 in the USPI

For more information on CRS grading and the CRS treatment algorithm, please refer to Table 1 in CARVYKTI® US Prescribing Information.

Considerations for monitoring

Monitor patients for signs and symptoms of CRS daily for 7 days at the Activated Treatment Center after CARVYKTI® infusion and periodically for 2 weeks for signs and symptoms of CRS:

- fever
- chills
- fatigue
- tachycardia
- headache
- hypotension
- hypoxia
- dizziness/lightheadedness
- organ toxicities

USPI=US Prescribing Information.

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

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Neurologic toxicities

Neurologic toxicities, which may be severe, life-threatening or fatal, occurred after CARVYKTI® infusion[1]

In CARTITUDE-4 and CARTITUDE-1 (N=285)

ANY GRADE	GRADE ≥3
24% (n=69/285)	**7%** (n=19/285)

Immune Effector Cell–Associated Neurotoxicity Syndrome (ICANS)

In CARTITUDE-4 and CARTITUDE-1 (N=285)

ANY GRADE	GRADE ≥3
13% (n=36/285)	**2%** (n=6/285)

In CARTITUDE-4 (N=188)

ANY GRADE	GRADE ≥3
7%	**0.5%**

In CARTITUDE-1 (N=97)

ANY GRADE	GRADE ≥3
23%	**3%**

- 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
- The most frequent (22%) 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 at the CARVYKTI® Activated Treatment Center 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

For more information on ICANS grading and the ICANS treatment algorithm, please refer to Table 2 in CARVYKTI® US Prescribing Information.

CRS=cytokine release syndrome; USPI=US Prescribing Information.

*See CARVYKTI® USPI Table 2 Guidance for management of ICANS.

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

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Additional potential neurologic toxicities

Parkinsonism

In CARTITUDE-4 and CARTITUDE-1 (N=285)

ANY GRADE	GRADE ≥3
3% (n=8/285)	**2%** (n=5/285)

In CARTITUDE-4 (N=188)

ANY GRADE	GRADE 3-4
1%	**0%**

In CARTITUDE-1 (N=97)

ANY GRADE	GRADE 3-4
6%	**4%**

- The 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 (GBS)

- 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

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

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Additional potential neurologic toxicities (cont)

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 immunoglobulin. Myelitis was ongoing at the time of death from other cause

Peripheral neuropathy

In CARTITUDE-4 and CARTITUDE-1 (N=285)

ANY GRADE	GRADE ≥3
7% (n=21/285)	**1%** (n=3/285)

In CARTITUDE-4 (N=188)

ANY GRADE	GRADE 3-4
7%	**0.5%**

In CARTITUDE-1 (N=97)

ANY GRADE	GRADE 3-4
7%	**2%**

- Monitor patients for signs and symptoms of peripheral neuropathies
- Patients who experience peripheral neuropathy may also experience cranial nerve palsies or GBS

GBS=Guillain-Barré syndrome.

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Additional potential neurologic toxicities (cont)

Cranial nerve palsies

In CARTITUDE-4 and CARTITUDE-1 (N=285)

ANY GRADE	GRADE ≥3
7% (n=19/285)	**1%** (n=1/285)

In CARTITUDE-4 (N=188)

ANY GRADE	GRADE 3-4
9%	**1%**

In CARTITUDE-1 (N=97)

ANY GRADE	GRADE 3-4
3%	**1%**

- 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

Patients should report signs or symptoms of neurologic toxicities including:

ICANS:
- aphasia
- encephalopathy
- depressed level of consciousness
- seizures
- delirium
- dysgraphia

Parkinsonism:
- tremor
- micrographia
- bradykinesia
- rigidity
- shuffling gait
- stooped posture
- masked facies
- apathy
- flat affect
- lethargy
- somnolence

Guillain-Barré Syndrome:
- motor weakness and polyradiculoneuritis

Peripheral neuropathy:
- peripheral motor and/or sensory nerve dysfunction

Cranial Nerve Palsies:
- facial paralysis
- facial numbness

ICANS=immune effector cell-associated neurotoxicity syndrome.

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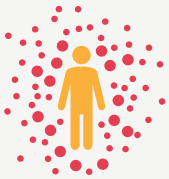
MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Hemophagocytic lymphohistiocytosis (HLH)



HLH is a potentially life-threatening complication.

In CARTITUDE-4 and CARTITUDE-1 (N=285)

ANY GRADE
1% (n=3/285)

- All events of HLH/MAS occurred in the setting of ongoing or worsening CRS

Considerations for monitoring and management

- 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

CRS=cytokine release syndrome; MAS=macrophage activation syndrome.

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Prolonged and/or recurrent cytopenias

Cytopenias develop as a result of lower-than-normal blood cell counts and are characterized by neutropenia or low neutrophils; thrombocytopenia or low blood platelet count; anemia or low red blood cell count; and lymphopenia or low lymphocytes.

- 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

Considerations for monitoring and management

Patients may exhibit prolonged and/or recurrent cytopenias for several weeks following lymphodepletion and CARVYKTI® infusion. One or more recurrence of Grade 3 or higher cytopenias may occur after partial or complete recovery of cytopenias. Counsel patients and care partners on how to reduce the risk of infection.

Monitor blood counts prior to and after CARVYKTI® infusion

For thrombocytopenia, consider supportive care with transfusions

Prolonged neutropenia has been associated with increased risk of infection

Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Immune Effector Cell-Associated Enterocolitis (IEC-EC)[1]

- Manifestations include severe or prolonged diarrhea, abdominal pain, and weight loss requiring total 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 postmarketing setting

Secondary malignancies

Patients treated with CARVYKTI® may develop secondary malignancies.

- The median time to onset of myeloid neoplasms was 447 days (range: 56 to 870 days) after treatment with CARVYKTI®
- 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)
- 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 postmarketing 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

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

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Preparing for potential serious infections

Severe, life-threatening, or fatal infections have occurred in patients receiving CARVYKTI®.

- Administer prophylactic, pre-emptive, and/or therapeutic antimicrobials according to the standard institutional guidelines
- CARVYKTI® should not be administered to patients with active infection or inflammatory disorders
- Monitor patients for signs and symptoms of infection before and after CARVYKTI® infusion and treat patients appropriately
- 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

BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; CD19=cluster of differentiation 19.

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MONITORING AND MANAGING SERIOUS ADVERSE REACTIONS

Other potential adverse reactions

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

Hypogammaglobulinemia may occur in patients receiving CARVYKTI®

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

Patients should be carefully monitored for 2 hours after infusion for signs and symptoms of **hypersensitivity** reactions

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia. Screen for infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing

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.

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

HBV=hepatitis B virus; IgG=immunoglobulin G; IVIG=intravenous immunoglobulin.

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

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Reporting adverse reactions

This guide is about identification of, and considerations for, managing adverse reactions associated with CARVYKTI®. To report suspected adverse reactions, contact Janssen Biotech, Inc., or the FDA.

REPORT SUSPECTED ADVERSE REACTIONS

Janssen Biotech, Inc.: 1-800-526-7736

FDA: 1-800-FDA-1088 (1-800-332-1088)

fda.gov/medwatch

FDA=U.S. Food and Drug Administration.

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

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Important Safety Information

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 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).

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Important Safety Information (cont)

WARNINGS AND PRECAUTIONS (cont)

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 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

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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.

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®.

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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 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.

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Important Safety Information (cont)

WARNINGS AND PRECAUTIONS (cont)

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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Communication and preparation are key with CARVYKTI®

Collaboration across patient care providers at Activated Treatment Centers and Primary Oncology Centers is essential for treatment success

Monitoring for signs and symptoms of adverse reactions, including delayed neurologic toxicities, is critical[a]

The **MyCARVYKTI® Patient Support Program**, sponsored by Janssen Biotech, Inc., and Legend Biotech, is designed to help eligible patients prescribed CARVYKTI® (ciltacabtagene autoleucel) and their care partners with support during treatment. To get your patients started, contact a **MyCARVYKTI® Patient Support Specialist** at **1-800-559-7875,** Monday to Friday, 8:00 AM to 8:00 PM ET

Online and live support for **CARVYKTI® Activated Treatment Centers** to streamline order management and fulfillment is available. To learn more, visit **CQUENCEPORTAL.com**, call **1-833-276-7337 (1-833-CQORDER)**, or contact your dedicated Cell Therapy Experience Leads (CTELs)

Learn more about CARVYKTI® at
CARVYKTIHCP.COM

[a]Refer to section 2.3 of the CARVYKTI® US Prescribing Information for complete guidelines on management of adverse reactions.

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Johnson&Johnson LEGEND BIOTECH

CARVYKTI® (ciltacabtagene autoleucel) Suspension for IV Infusion