CARVYKTI® (ciltacabtagene autoleucel) Training Module:

Select Adverse Reactions including Cytokine Release Syndrome (CRS), Immune Effector Cell-associated Enterocolitis (IEC-EC), and Neurologic Toxicities including Immune Effector Cell-associated Neurotoxicity Syndrome (ICANS)

Please see full Prescribing Information, including Boxed Warning, available at this presentation.

Johnson&Johnson

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CARVYKTI® Training Module

- This educational module contains information on select adverse reactions associated with CARVYKTI®, including CRS and neurologic toxicities
- These are not all the adverse reactions associated with CARVYKTI®. Please refer to the CARVYKTI® Prescribing Information/Medication Guide for more information

Unless specifically referenced, all information in this education module is found in:
CARVYKTI® Prescribing Information and Medication Guide. Horsham, PA: Janssen Biotech, Inc.

CRS, cytokine release syndrome.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

CARVYKTI® Indication

Relapsed or refractory multiple myeloma

CARVYKTI® is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 1 prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide

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

Cytokine Release Syndrome (CRS) and Neurologic Toxicities Including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

CARVYKTI® Boxed Warning

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 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®.

BCMA, B-cell maturation antigen; CD, cluster of differentiation; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; MAS, macrophage activation syndrome.

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

Pivotal Studies

- CARTITUDE-1 (N=97) is a Phase 1b/2 open-label, single-arm, multicenter trial in adult patients with RRMM, who previously received at least three prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody
- CARTITUDE-4 (N=419) is a Phase 3 randomized, open-label, multicenter trial evaluating the efficacy of CARVYKTI® for the treatment of adult patients with relapsed and lenalidomide-refractory MM, who previously received at least one prior line of therapy including a proteasome inhibitor and an immunomodulatory agent
- The safety data described in the WARNINGS and PRECAUTIONS section reflect exposure to CARVYKTI® in 285 patients with relapsed or refractory multiple myeloma: one randomized, open label with 188 patients in CARTITUDE-4 and one single-arm, open label study with 97 patients in CARTITUDE-1.

CD, cluster of differentiation; MM, multiple myeloma; RRMM, relapsed/refractory multiple myeloma.
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Preparing the Patient for CARVYKTI® Infusion

- Confirm availability of CARVYKTI® prior to starting the lymphodepleting chemotherapy regimen
- Administer the lymphodepleting chemotherapy regimen: cyclophosphamide 300 mg/m^2 IV and fludarabine 30 mg/m^2 IV daily for 3 days
- See the prescribing information of cyclophosphamide and fludarabine for information on dose adjustment in renal impairment
- Lymphodepleting regimen must be delayed if a patient has serious adverse reactions from preceding bridging therapies (including clinically significant active infection, cardiac toxicity, and pulmonary toxicity) or active graft versus host disease in patients with prior allogeneic stem cell transplant
- Consider repeating lymphodepleting regimen if CARVYKTI® dosing is delayed by more than 14 days and patient has recovered from toxicity of the first lymphodepleting regimen
- Administer CARVYKTI® infusion 2 to 4 days after the completion of the lymphodepleting chemotherapy regimen
- CARVYKTI® infusion should be delayed if a patient has any of the following conditions:
  - Clinically significant active infection or inflammatory disorders
  - Grade ≥3 non-hematologic toxicities of cyclophosphamide and fludarabine conditioning, except for Grade 3 nausea, vomiting, diarrhea, or constipation. CARVYKTI® infusion should be delayed until resolution of these events to Grade ≤1

IV, intravenous.

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Cytokine Release Syndrome (CRS)

- CRS, including fatal or life-threatening reactions, occurred following treatment with CARVYKTI®[1]
- In CARTITUDE-1 and CARTITUDE- 4, CRS was graded using ASTCT 2019[2] criteria which is different from the 2014 Lee criteria[3]
- Specifically, organ toxicity associated with CRS is not captured by 2019 ASTCT criteria; only fever, hypoxia and hypotension are considered for grading[2,3]
- 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[1]

ASTCT, American Society for Transplantation and Cellular Therapy.

1. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. 2. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625–638.
3. Lee DW, et al. *Blood.* 2014;124:188–195.

Cytokine Release Syndrome (CRS)

CARTITUDE-1 and CARTITUDE-4 (n=285)

- CRS was reported in the majority (84% [238/285]) of patients
  - Grade ≥3 CRS: 4% (11/285)
- The median time to onset of CRS of any grade was 7 days (range: 1–23)
- CRS resolved in 82% of patients with a median duration of 4 days (range: 1–97)
- The most common manifestations of CRS in all patients combined (≥10%) included:
  - Fever (84%)
  - Hypotension (29%)
  - Aspartate aminotransferase increased (11%)

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

Management of CRS in CARTITUDE-1 and CARTITUDE-4

CARTITUDE-1 and CARTITUDE-4 (n=285)

- Tocilizumab treatment
  - 53% (150/285) of patients received tocilizumab
    - 35% (100/285) received a single dose
    - 18% (50/285) received more than one dose of tocilizumab
- Corticosteroid treatment
  - 14% (39/285) of patients received at least one dose of corticosteroids for treatment of CRS

CRS, cytokine release syndrome.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

Clinical Signs and Symptoms of CRS

- Patients should be closely monitored for signs or symptoms of CRS, including fever
- Refractory CRS is characterized by fevers, end-organ toxicity (e.g., hypoxia, hypotension) not improving within 12 hours of first line interventions or development of HLH/MAS
- Potentially life-threatening complications of CRS include HLH

Signs and symptoms may include but are not limited to:

- Fever
- Chills
- Fatigue
- Headache
- Tachycardia
- Hypotension
- Hypoxia
- Dizziness/lightheadedness
- Organ toxicities

CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

Risk Factors for Severe CRS

- According to literature reports, the severity of CRS has been related to:
  - High pre-infusion tumor burden[1–3]
  - Active infection[3,4] and early onset of fever[5]
  - Persistent fever after symptomatic treatment[5,6]

For patients experiencing ANY of the above, early use (Grade 1 CRS) of tocilizumab may be considered.
Refer to the CARVYKTI® USPI[7] for additional information

CRS, cytokine release syndrome; USPI, United States Prescribing Information.

1. Neelapu S, et al. *Hematol Oncol*. 2019;37:48–52. 2. Brudno JN, et al. *Blood*. 2016;127:3321–3330. 3. Hay KA, et al. *Br J Haematol*. 2018;183:364–374.
4. Korell F, et al. *Cancers (Basel)*. 2021;13:1684. 5. Hay KA, et al. *Blood*. 2017;130:2295–2306. 6. Davila ML, et al. *Sci Transl Med*. 2014;6:224ra25.
7. CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

CRS Management

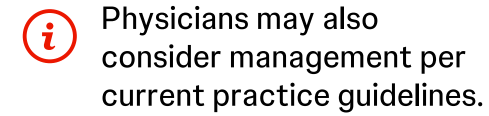
- Identify CRS based on clinical presentation and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids
- Evaluate for and treat other causes of fever, hypoxia and hypotension
- Consider laboratory testing to monitor for DIC and hemorrhage, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function
- Patients who experience CRS should be closely monitored for cardiac and other organ function until resolution of symptoms. Consider anti-seizure prophylaxis with levetiracetam in patients who experience CRS
- Patients who experience Grade 2 or higher CRS (eg, hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous telemetry and pulse oximetry
- For severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy
- 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
  - 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
  - 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
- For CRS refractory to first line interventions such as tocilizumab or tocilizumab and corticosteroids, consider alternate treatment options (ie, higher corticosteroid dose, alternative anti-cytokine agents, eg, anti-IL1 and/or anti-TNFα, anti-T-cell therapies)

Refer to the CARVYKTI® USPI for additional information

CRS, cytokine release syndrome; DIC, disseminated intravascular coagulation; HLH, hemophagocytic lymphohistiocytosis; IL, interleukin; MAS, macrophage activation syndrome; TNFα, tumor necrosis factor alpha; USPI, United States Prescribing Information.

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

CRS Management Guide (Table 1 in USPI)



CRS grade*	Tocilizumab†/Corticosteroids‡
Grade 1 Temperature ≥38°C§ (100.4°F)	In patients with: • Early onset of fever (if onset less than 72 hours after infusion) Tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) may be considered Corticosteroids: N/A
Grade 2 Symptoms require and respond to moderate intervention. Temperature ≥38°C§ (100.4°F) with: Hypotension not requiring vasopressors, and/or, Hypoxia requiring oxygen via cannula¶ or blow-by, or, Grade 2 organ toxicity**	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids up to 1 L or increasing supplemental oxygen Consider dexamethasone 10 mg IV every 12–24 hours If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6–12 hours) If no improvement within 24 hours or rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours After two doses of tocilizumab, consider alternative anti-cytokine agents†† Do not exceed three doses of tocilizumab in 24 hours, or four doses in total

*Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity. †Refer to tocilizumab prescribing information for details. ‡Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is >3 days. §Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (eg, tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause. ¶Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min. **Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. ††Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; IV, intravenous; USPI, United States Prescribing Information.

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

CRS Management Guide (Table 1 in USPI)

Presenting symptoms*	Tocilizumab†/Corticosteroids‡
Grade 3 Symptoms require and respond to aggressive intervention Temperature ≥38°C§ (100.4°F) with: Hypotension requiring one vasopressor with or without vasopressin, and/or, Hypoxia requiring oxygen via high-flow nasal cannula¶, facemask, non-rebreather mask, or Venturi mask, or, Grade 3 organ toxicity or Grade 4 transaminitis	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids up to 1 L or increasing supplemental oxygen Consider dexamethasone 10 mg IV every 12–24 hours If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours) If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours After two doses of tocilizumab, consider alternative anti-cytokine agents** Do not exceed three doses of tocilizumab in 24 hours, or four doses in total

*Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity. †Refer to tocilizumab prescribing information for details. ‡Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is >3 days. §Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (eg, tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause. ¶Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min. **Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; IV, intravenous; USPI, United States Prescribing Information.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

CRS Management Guide (Table 1 in USPI)

Presenting symptoms*	Tocilizumab†/Corticosteroids‡
Grade 4 Life-threatening symptoms Requirements for ventilator support, continuous veno-venous hemodialysis Temperature ≥38°C§ (100.4°F) with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminitis)	Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg) Repeat tocilizumab every 8 hours as needed if not responsive to IV fluids up to 1 L or increasing supplemental oxygen Administer dexamethasone 20 mg IV every 6 hours After two doses of tocilizumab, consider alternative anti-cytokine agents¶ Do not exceed three doses of tocilizumab in 24 hours, or four doses in total If no improvement within 24-hours consider methylprednisolone (1–2 g IV, repeat every 24 hours if needed; taper as clinically indicated) or other immunosuppressants (eg, other anti-T cell therapies)

*Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity. †Refer to tocilizumab prescribing information for details. ‡Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is >3 days. §Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia, as it may be masked by interventions such as antipyretics or anti-cytokine therapy (eg, tocilizumab or steroids). Absence of fever does not impact CRS management decision. In this case, CRS management is driven by hypotension and/or hypoxia and by the more severe symptom not attributable to any other cause. ¶Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; IV, intravenous; USPI, United States Prescribing Information.

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

Neurologic Toxicities

CARTITUDE-1 and CARTITUDE-4 (n=285)

- Neurologic toxicities, which may be severe, life-threatening, or fatal, occurred in 24% of patients (69/285) following treatment with CARVYKTI®
  - Grade ≥3 neurologic toxicities occurred in 7% (19/285) of patients
- Neurologic toxicities included:
  - ICANS 13%
  - Peripheral neuropathy 7%
  - Cranial nerve palsies 7%
  - Parkinsonism 3%
  - Immune mediated myelitis 0.4%
  - Guillain-Barré Syndrome (GBS)
- The median time to onset was 10 days (range: 1–101) 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: 1–544)
- Ninety-six percent of patients with neurologic toxicities (66/69) also developed CRS

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

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

Neurologic Toxicities: ICANS

In CARTITUDE-1 and CARTITUDE-4, ICANS was graded using ASTCT 2019 criteria, which is based on the following components:

- ICE score
- Depressed level of consciousness
- Seizure
- Motor findings
- Raised intracranial pressure/cerebral edema

Symptoms include but are not limited to:

- Aphasia
- Encephalopathy
- Depressed level of consciousness
- Seizures
- Delirium
- Dysgraphia

ASTCT, American Society for Transplantation and Cellular Therapy; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune-effector cell-associated encephalopathy.
Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25:625–638.

Immune Cell-Associated Neurologic Syndrome (ICANS)

The onset of ICANS can occur at any time:

- Prior to onset of CRS
- Concurrent with CRS
- Following resolution of CRS
- In the absence of CRS

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
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Immune Cell-Associated Neurologic Syndrome (ICANS)

CARTITUDE-1 and CARTITUDE-4 (n=285)

- ICANS occurred in 13% (36/285) of the patients
  - Grade ≥3 in 2% (6/285) of the patients
- The median time to onset of ICANS was 8 days (range: 1–28)
- ICANS resolved in 30 of 36 (83%) of patients with a median time to resolution of 3 days (range: 1–143)
  - The median duration of ICANS was 6 days (range: 1–1229)
- 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

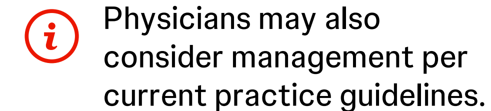
CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

ICANS Management

- Monitor patients at least daily for 7 days following CARVYKTI® infusion for signs and symptoms of ICANS
- Monitor patients for signs or symptoms of ICANS for 2 weeks after infusion
- Counsel patients to seek immediate medical attention should signs and symptoms of neurotoxicity occur after recovery from CRS and/or ICANS
- At the first sign of ICANS, immediately evaluate the patient for hospitalization and institute treatment with supportive care
- Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; REMS, Risk Evaluation Mitigation Strategy.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

ICANS Management Guide (Table 2 in USPI)



ICANS grade*	Corticosteroids
Grade 1 ICE score 7–9† or depressed level of consciousness: awakens spontaneously	Consider dexamethasone‡ 10 mg IV every 12–24 hours for 2 to 3 days Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis
Grade 2 ICE score 3–6† or depressed level of consciousness: awakens to voice	Administer dexamethasone‡ 10 mg IV every 12 hours for 2–3 days, or longer for persistent symptoms Consider steroid taper if total corticosteroid exposure is >3 days If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis
Grade 3 ICE score 0–2† (If ICE score is 0, but the patient is arousable (eg, awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, or seizures, either: • Any clinical seizure, focal or generalized, that resolves rapidly, or • Non-convulsive seizures on EEG that resolve with intervention, or raised ICP: focal/local edema on neuroimaging§	Administer dexamethasone‡ 10–20 mg IV every 6 hours If no improvement after 24 hours or worsening of neurologic toxicity, escalate dexamethasone‡ dose to at least 20 mg IV every 6 hours, OR escalate to high-dose methylprednisolone (1–2 g/day, repeat every 24 hours if needed; taper as clinically indicated) Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1–2 g, repeat every 24 hours if needed; taper as clinically indicated)

Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.
*ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al., 2019).
†If patient is arousable and able to perform ICE assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name three objects, eg, point to clock, pen, button = 3 points); Following Commands (eg, 'show me 2 fingers' or 'close your eyes and stick out your tongue' = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by 10 = 1 point). If patient is unarousable and unable to perform ICE assessment (Grade 4 ICANS) = 0 points. ‡All references to dexamethasone administration are dexamethasone or equivalent. §Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to NCI CTCAE v5.0.
ASTCT, American Society for Transplantation and Cellular Therapy; EEG, electroencephalogram; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune-effector cell-associated encephalopathy; ICP, intracranial pressure; IV, intravenous; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

ICANS Management Guide (Table 2 in USPI)

ICANS grade*	Corticosteroids
Grade 4 ICE score 0† (Patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness either: • Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • Stupor or coma, or seizures, either: • Life-threatening prolonged seizure (>5 min), or • Repetitive clinical or electrical seizures without return to baseline in between, or motor findings‡: • Deep focal motor weakness such as hemiparesis or paraparesis, or raised ICP/cerebral edema, with signs/symptoms such as: • Diffuse cerebral edema on neuroimaging, or • Decerebrate or decorticate posturing, or • Cranial nerve VI palsy, or • Papilledema, or • Cushing's triad	Administer dexamethasone§ 20 mg IV every 6 hours If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1–2 g/day, repeated every 24 hours if needed; taper as clinically indicated) Consider non-sedating, anti-seizure medicines (eg, levetiracetam) for seizure prophylaxis If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1–2 g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation

Note: ICANS grade and management is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema), not attributable to any other cause.
*ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al., 2019). †If patient is arousable and able to perform ICE assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name three objects, eg, point to clock, pen, button = 3 points); Following Commands (eg, 'show me 2 fingers' or 'close your eyes and stick out your tongue' = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points. ‡Tremors and myoclonus associated with immune effector cell therapies may be graded according to NCI CTCAE v5.0, but they do not influence ICANS grading. §All references to dexamethasone administration are dexamethasone or equivalent.
ASTCT, American Society for Transplantation and Cellular Therapy; ICANS, immune effector cell-associated neurotoxicity syndrome; ICE, immune-effector cell-associated encephalopathy; ICP, intracranial pressure; IV, intravenous; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

Parkinsonism

CARTITUDE-1 and CARTITUDE-4 (n=285)

- Parkinsonism occurred in 3% (8/285) of the patients
  - Grade ≥3 in 2% (5/285)
- The median time to onset of parkinsonism was 56 days (range: 14–914)
- Parkinsonism resolved in one of eight (13%) of patients with a median time to resolution of 523 days
- The median duration of parkinsonism was 243.5 days (range: 62–720)
- The onset of parkinsonism occurred after CRS for all patients and after ICANS for six 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)

CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
CARVYKTI® [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc.

Peripheral Neuropathy

CARTITUDE-1 and CARTITUDE-4 (n=285)

Peripheral neuropathy occurred following treatment with CARVYKTI®

- Peripheral neuropathy occurred in 7% (21/285) of the patients
  - Grade ≥3 in 1% (3/285)
- The median time to onset was 57 days (range: 1–914)
- Peripheral neuropathy resolved in 11 of 21 (52%) of patients with a median time to resolution of 58 days (range: 1–215)
- The median duration of peripheral neuropathy was 149.5 days (range: 1–692)
- 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)

Patients who experienced peripheral neuropathy may also experience cranial nerve palsies or Guillain-Barré syndrome.
Monitor patients for signs and symptoms of peripheral neuropathies

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Cranial Nerve Palsies

CARTITUDE-1 and CARTITUDE-4 (n=285)

Patients may experience cranial nerve palsies following CARVYKTI® infusion

- Cranial nerve palsies occurred in 7% (19/285) of the patients
  - Grade ≥3 in 1% (1/285)
- The median time to onset of cranial nerve palsies was 21 days (range: 17–101)
- Cranial nerve palsies resolved in 17 of 19 (89%) of patients with a median time to resolution of 66 days (range: 1–209)
- The median duration of cranial nerve palsies was 70 days (range: 1–262)
- 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

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

Immune Mediated Myelitis

Grade 3 myelitis has 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

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

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

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

Immune Effector Cell-associated Enterocolitis (IEC-EC)

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 postmarketing setting

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

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Patient and Care Partner Education

- Advise patients and their care partners of the risks of CRS and neurologic toxicities and to contact their healthcare professional if the patient is experiencing signs or symptoms associated with CRS and neurologic toxicities
- Patients should be monitored daily for 7 days following the infusion and then periodically for 2 weeks
- It is recommended that patients remain close to the location where treatment was received for at least 2 weeks following infusion
- Before discharge, the patients or care partners should be provided with the *Patient Wallet Card*
- The *Patient Wallet Card* reminds them of the signs and symptoms of CRS and neurologic toxicities that require immediate medical attention
- Patients receiving CARVYKTI® are at risk for altered or decreased consciousness or coordination in the 2 weeks following 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 symptoms

CRS, cytokine release syndrome.

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

Adverse Event Reporting

Reporting of suspected adverse events after administration of therapy is vital for the continued monitoring of the risk/benefit balance of therapy

To report any serious adverse events* suggestive of CRS or neurologic toxicities contact Janssen Biotech, Inc., at 1-800-526-7736 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Healthcare providers are also encouraged to report any suspected serious adverse events associated with CARVYKTI® as detailed above

*Serious adverse events are defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
CRS, cytokine release syndrome; FDA, Food and Drug Administration.

CARVYKTI® Important Safety Information (ISI)

Relapsed or refractory multiple myeloma

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

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CARVYKTI® Important Safety Information (ISI)

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®.

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

Proactive Use, Not for Distribution

CARVYKTI® Important Safety Information (ISI)

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.

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.

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

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CARVYKTI® Important Safety Information (ISI)

Warnings and Precautions (cont)

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.

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Proactive Use, Not for Distribution

CARVYKTI® Important Safety Information (ISI)

Warnings and Precautions (cont)

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 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.

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

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CARVYKTI® Important Safety Information (ISI)

Warnings and Precautions (cont)

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®.

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.

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CARVYKTI® Important Safety Information (ISI)

Warnings and Precautions (cont)

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.

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CARVYKTI® Important Safety Information (ISI)

Warnings and Precautions (cont)

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.

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.

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CARVYKTI® Important Safety Information (ISI)

Warnings and Precautions (cont)

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.

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

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