CARVYKTI® (ciltacabtagene autoleucel) suspension for intravenous infusion

Initial U.S. Approval: 2022

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

WARNINGS AND PRECAUTIONS

5.1 Cytokine Release Syndrome

Severe or life-threatening reactions, occurring in patients following treatment with CARVYKTI. Do not administer CARVYKTI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids. (2.2, 2.3, 5.1)

5.2 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. (5.5)

5.3 Secondary Hematological Malignancies

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred following treatment with CARVYKTI. (5.6, 6.1)

5.4 CARVYKTI REMS

CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS. (5.4)

DOSE FORMS AND STRENGTHS

For autologous use only. For intravenous use only.

• Administer a lymphodepleting regimen of cyclophosphamide and fludarabine before infusion of CARVYKTI. (2.2)
• Do NOT use a leukodepleting filter. (2.2)
• Verify the patient’s identity prior to infusion. (2.2)

CONTRAINDICATIONS

None (4)

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

See full prescribing information for complete boxed warning.

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

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

• Parkinsonism and Guillain-Barré syndrome and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVYKTI. (5.2)

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

• Prolonged and/or recurrent cytopenias with bleeding and infection and requirement for stem cell transplantation for hematopoietic recovery occurred following treatment with CARVYKTI. (5.5)

• Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred following treatment with CARVYKTI. (5.6, 6.1)

CARVYKTI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CARVYKTI REMS. (5.4)

For autologous use only. For intravenous use only.

• Premedicate with acetaminophen and an H1-antihistamine. (2.2)

• Avoid prophylactic use of systemic corticosteroids. (2.2)

• Confirm availability of tocilizumab prior to infusion. (2.2, 5.1)

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

CARVYKTI® (cilta-cabtagene autoleucel) suspension for intravenous infusion

16 HOW SUPPLIED/STORAGE AND HANDLING

CARVYKTI® (cilta-cabtagene autoleucel) suspension for intravenous infusion contains 0.5-1.0×10^6 CAR-positive viable T cells per kg body weight, with a maximum dose of 1×10^8 CAR-positive viable T cells per single-dose infusion. (2.1)

17 PATIENT COUNSELING INFORMATION

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

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

1 INDICATIONS AND USAGE

For autologous use only. For intravenous use only.

• Premedicate with acetaminophen and an H1-antihistamine. (2.2)

• Avoid prophylactic use of systemic corticosteroids. (2.2)

• Confirm availability of tocilizumab prior to infusion. (2.2, 5.1)

• Dosing of CARVYKTI is based on the number of chimeric antigen receptor (CAR)-positive viable T cells. (2.1)

• Recommended dose range is 0.5-1.0×10^6 CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10^8 CAR-positive viable T cells per single-dose infusion. (2.1)

• Administer CARVYKTI at a REMS-certified healthcare facility. (2.2)

• CARVYKTI is a cell suspension for intravenous infusion. (3)

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

• Cytokine Release Syndrome (CRS), including fatal or life-threatening, occurred following treatment with CARVYKTI. Provide supportive care and/or corticosteroids which may be fatal or life-threatening, occurred following treatment with CARVYKTI. (5.1)

• Hypersensitivity Reactions: Hypersensitivity reactions have occurred. Monitor for hypersensitivity reactions during infusion. (5.7)

• Secondary Malignancies: Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred. In the event that a secondary malignancy occurs after treatment with CARVYKTI, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN). (5.9)

• Effects on Ability to Drive and Use Machines: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving CARVYKTI and in the event of any new onset of neurologic toxicities. (5.10)

The most common nonlaborable adverse reactions (incidence greater than 20%) are pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections-pathogen unspecified, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dyspnea, edema, viral infections, coagulopathy, constipation, and vomiting. The most common laboratory adverse reactions (incidence greater than or equal to 50%) include thrombocytopenia, coagulopathy, anemia, neutropenia, and lymphopenia. (5.10)

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2023

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1 INDICATIONS AND USAGE
CARVYKTI® is a B-cell maturation antigen (BCMA)-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including before CRS onset, concurrently with CRS, after CRS resolution, or during cytokine release syndrome (CRS), including fatal or life-threatening reactions, including those requiring tocilizumab or tocilizumab and corticosteroids [see Warnings and Precautions (5.3)].

2 DOSAGE AND ADMINISTRATION
For autologous use only. For intravenous use only.

2.1 Dose
CARVYKTI is provided as a single dose for infusion containing a suspension of chimeric antigen receptor (CAR)-positive viable T cells in one infusion bag. A recommended dose range is 0.5-1.0×10⁶ CAR-positive viable T cells per kg of body weight, with a maximum dose of 1×10⁸ CAR-positive viable T cells per single infusion.

2.2 Administration
CARVYKTI is administered by intravenous infusion over a period of 30 minutes. Do not re-freeze or refrigerate thawed product.
CARVYKTI® (cilta-cabtagene autoleucel)

Monitoring After Infusion
Administer CARVYKTI at a REMS-certified healthcare facility.
Monitor patients at least daily for 10 days following CARVYKTI infusion at a certified healthcare facility for signs and symptoms of cytokine release syndrome (CRS) and neurologic toxicities. Monitor periodically for 4 weeks for signs and symptoms of delayed neurologic toxicity.
Instruct patients to remain within proximity of a certified healthcare facility for at least 4 weeks following infusion.
Instruct patients to refrain from driving or hazardous activities for at least 8 weeks following infusion.

2.3 Management of Severe Adverse Reactions
Cytokine Release Syndrome
Identify CRS based on clinical presentation [see Warnings and Precautions (5.1)]. Evaluate for and treat other causes of fever, hypoxia and hypotension. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematologic parameters, as well as pulmonary, cardiac, renal, and hepatic function. If CRS is suspected, manage according to the recommendations in Table 1.
Patients who experience CRS should be closely monitored for cardiac and other organ function until resolution of symptoms. Consider anti-seizure prophylaxis with levetiracetam in patients who experience CRS.

Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous telemetry and pulse oximetry.
For severe or life-threatening CRS, consider intensive care unit level monitoring and supportive therapy.
For CRS refractory to first line interventions such as tocilizumab or tocilizumab and corticosteroids, consider alternate treatment options (i.e., higher corticosteroid dose, alternative anti-cytokine agents, e.g., anti-IL1 and/or anti-TNFx, anti-T cell therapies). Refractory CRS is characterized by fevers, end-organ toxicity (e.g., hypoxia, hypotension) not improving within 12 hours of first line interventions or development of HLH/MAS.

If concurrent neurologic toxicity is suspected during CRS, administer:
- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to the CRS grade in Table 1
- Anti-seizure medication according to the neurologic toxicity in Table 2

Table 1: CRS Grading and Management Guidance

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Temperature ≥38°Cc</td>
<td>In patients with:</td>
<td></td>
</tr>
<tr>
<td>• Early onset of fever (if onset less than 72 hours after infusion)</td>
<td>Tocilizumab 8 mg/kg intravenously (IV) over 1 hour (not to exceed 800 mg) may be considered</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>Administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids up to 1 liter or increasing supplemental oxygen.</td>
<td>Consider dexamethasone 10 mg IV every 12-24 hours.</td>
</tr>
<tr>
<td>Symptoms require and respond to moderate intervention. Temperature ≥38°Cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension not requiring vasopressors, and/or, Hypoxia requiring oxygen via canulae or blow-by, or, Grade 2 organ toxicity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>If no improvement within 24 hours or rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td>
<td></td>
</tr>
<tr>
<td>Symptoms require and respond to aggressive intervention. Temperature ≥38°Cc 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 transaminisits.</td>
<td>If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (20 mg IV every 6 to 12 hours). If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours. After 2 doses of tocilizumab, consider alternative anti-cytokine agents. Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>Per Grade 2</td>
<td>Administer dexamethasone 10 mg IV every 12 hours.</td>
</tr>
<tr>
<td>Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD). Temperature ≥38°Cc with: Hypotension requiring multiple vasopressors (excluding vasopressin), and/or, Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation), or, Grade 4 organ toxicity (excluding transaminisits).</td>
<td>Per Grade 2</td>
<td>Administer dexamethasone 20 mg IV every 6 hours.</td>
</tr>
</tbody>
</table>

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

Neurologic Toxicities
Monitor patients for signs and symptoms of neurologic toxicities (ICANS and other neurologic toxicities) [see Warnings and Precautions (5.2)]. Rule out other causes of neurologic signs or symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities. Please see section 5.2 for non ICANS neurologic toxicities. If ICANS is suspected, manage according to the recommendations in Table 2.
If concurrent CRS is suspected during the neurologic toxicity event, administer:
- Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in Tables 1 and 2
- Tocilizumab according to CRS grade in Table 1
- Anti-seizure medication according to neurologic toxicity in Table 2

Table 1: CRS Grading and Management Guidance (continued)
CARVYKTI® (ciltacabtagene autoleucel)

Table 2: Guideline for management of ICANS

<table>
<thead>
<tr>
<th>ICANS Gradea</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td>ICE score 7-9b or depressed level of consciousness; awaken spontaneously.</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>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 greater than 3 days.</td>
</tr>
<tr>
<td>ICE score 3-6b or depressed level of consciousness; awaken to voice</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>Administer dexamethasone 10 mg-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 (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td>ICE score 0-2c (If ICE score is 0, but the patient is arousable, awake with global aphasia and able to perform assessment)</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>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 (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td>ICE score 0 (Patient is unarousable and unable to perform ICE assessment) or depressed level of consciousness;</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>If cerebral edema is suspected, consider hyperventilation and hypersomolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated).</td>
</tr>
<tr>
<td>IOCANS (ICANS) Gradea Corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Grade 5</td>
<td>Administer dexamethasone 10 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 (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td>ICE score 7-9b or depressed level of consciousness; awaken spontaneously.</td>
<td></td>
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<tr>
<td>Grade 4</td>
<td>Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td>ICE score 3-6b or depressed level of consciousness; awaken to voice</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>If cerebral edema is suspected, consider hyperventilation and hypersomolar therapy. Give high-dose methylprednisolone (1-2 g, repeat every 24 hours if needed; taper as clinically indicated). Consider neurology and/or neurosurgery consultation.</td>
</tr>
<tr>
<td>ICE score 0-2c (If ICE score is 0, but the patient is arousable, awake with global aphasia and able to perform assessment)</td>
<td></td>
</tr>
</tbody>
</table>

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.

CARVYKTI® (ciltacabtagene autoleucel)

- ASTCT 2019 criteria for grading Neurologic Toxicity (Lee et al, 2019).
- If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital = 4 points); Naming (name 3 objects, e.g., point to clock, pen, button = 3 points); Following Commands (e.g., “show me 2 fingers” or “close your eyes and stick out your tongue” = 1 point); Writing (ability to write a standard sentence = 1 point); and Attention (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
- 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.
- Tremors and myoclonus associated with immune effector cell therapies may be graded according to NCI CTCAE v6.0, but they do not influence ICANS grading.

3. DOSAGE FORMS AND STRENGTHS
CARVYKTI is a cell suspension for intravenous infusion.

A single dose of CARVYKTI contains a cell suspension of 0.5-1.0×10⁹ CAR-positive viable T cells per kg body weight in one infusion bag up to a maximum of 1×10⁹ CAR-positive viable T cells [see How Supplied/Storage and Handling (16)].

4. CONTRAINDICATIONS
None.

5. WARNINGS AND PRECAUTIONS
5.1 Cytokine Release Syndrome
Cytokine release syndrome, including fatal or life-threatening reactions, occurred following treatment with CARVYKTI. CRS occurred in 85% (92/107) of patients receiving ciltacabtagene autoleucel. Grade 3 or higher CRS (2019 ASTCT grade) occurred in 5% (5/97) of patients, with Grade 5 CRS reported in 1 patient. The median time to onset of CRS was 7 days (range: 1 to 12 days). The median duration of CRS was 4 days (range: 1 to 40 days) in all but one patient who had a duration of CRS of 97 days at a subsequent fatal outcome. In patients who experienced CRS, the most common manifestations of CRS included pyrexia (100%), hypotension (45%), increased aspartate aminotransferase (AST) (22%), chills (15%), increased alanine aminotransferase (ALT) (14%) and sinus tachycardia (11%). Grade 3 or higher events associated with CRS included increased AST and ALT, hyperbilirubinemia, hypotension, pyrexia, hypoxia, respiratory failure, acute kidney injury, disseminated intravascular coagulation and hemorrhage, HLH/MAS, angina pectoris, supraventricular and ventricular tachycardia, malaise, myalgias, increased-C-reactive protein, fever, blood alkaline phosphatase and gamma-glutamyl transferase [see Adverse Reactions (6.1)].

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. CRS has been reported to be associated with findings of HLH/MAS, and the physiology of the syndromes may overlap. HLH/MAS is a potentially life-threatening condition. In patients with progressive symptoms of CRS or refractory CRS despite treatment, evaluate for evidence of HLH/MAS.

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

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

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

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

Overall, one or more subtypes of neurologic toxicity described below occurred following ciltacabtagene autoleucel infusion in 26% (25/97) of patients of which 11% (11/97) of patients experienced Grade 3 or higher events. These subtypes of neurologic toxicities were also observed in 2 ongoing studies [see Adverse Reactions (6.1)].
CARVYKTI® (ciltaacetab gene autoleucel)

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 during prolonged thrombocytopenia. ICANS occurring after treatment with CARVYKTI is distinct from ICANS occurring after treatment with other cancer immunotherapies, including those in ongoing trials of ciltaacetab gene autoleucel. ICANS occurred during CRS in 18 patients, before the onset of CRS in 2 patients, and after the CRS event in 3 patients.

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

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

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

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

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

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

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

5.4 CARVYKTI REMS

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

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

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

5.5 Prolonged and Recurrent Cytopenias

Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI infusion. In Study CARTITUDE-1 (N=97), 30% (29/97) of patients experienced prolonged Grade 4 cytopenia in one or more of the following treatments attempted in one or more patients – systemic chemotherapy, intravenous immunoglobulins. Symptoms reported include those consistent with Miller-Fisher variant of GBS, encephalopathy, motor weakness, speech disturbances, and polyradiculoneuritis.

Monitor for GBS. Evaluate patients presenting with peripheral neuropathy for GBS. Consider treatment of GBS with supportive care measures and in conjunction with immunoglobulins and plasma exchange, depending on severity of GBS.

Immune Mediated Myelitis

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

Monitor patients for signs and symptoms of peripheral neuropathies.
CARVYKTI® (ciltaceptagene autoleucel)

Grade 5 infections reported in other studies with CARVYKTI include bronchopulmonary aspergillosis, pneumocystis jirovecii pneumonia, and CMV colitis (with HSV-1 hepatitis). Another patient developed mycotic aneurysm due to cerebral mycotic abscess and died of subarachnoid hemorrhage. Monitor patients for signs and symptoms of infection before and after CARVYKTI infusion and treat patients appropriately. Administer prophylactic, pre-emptive and/or therapeutic antimicrobials according to the standard institutional guidelines. Febrile neutropenia was observed in 10% of patients after ciltaceptagene autoleucel infusion and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad-spectrum antibiotics, fluids and other supportive care, as medically indicated.

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

Viral Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients with hypogammaglobulinemia. Perform screening for cytomegalovirus (CMV), HBV, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) or any other infectious agents if clinically indicated in accordance with clinical guidelines before collection of cells for manufacturing. Consider antiviral therapy to prevent viral reactivation per local institutional guidelines/clinical practice.

Use of Live Vaccines

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

5.8 Hypersensitivity Reactions

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

5.9 Secondary Malignancies

Patients treated with CARVYKTI may develop secondary malignancies. Myeloid neoplasms (five cases of myelodysplastic syndrome, three cases of acute myeloid leukemia and two cases of myelodysplastic syndrome followed by acute myeloid leukemia) each occurred in 10% (10/97) of patients in CARTITUDE-1 study following treatment with CARVYKTI. The median time to onset of myeloid neoplasms was 485 days (range: 162 to 1040 days) after treatment with CARVYKTI. Nine of these 10 patients died following the development of myeloid neoplasms; Four of the 10 cases of myeloid neoplasms occurred after initiation of subsequent antimyeloma therapy. Cases of myelodysplastic syndrome and acute myeloid leukemia have also been reported in the post marketing setting. 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.

5.10 Effects on Ability to Drive and Use Machines

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

6 ADVERSE REACTIONS

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

- Cytokine Release Syndrome [see Warnings and Precautions (5.1)].
- Neurologic Toxicities [see Warnings and Precautions (5.2)].
- Hemophagocytic Lymphohistiocytosis (HLH)/Macrophage Activation Syndrome (MAS) [see Warnings and Precautions (5.3)].
- Prolonged and Recurrent Cytopenias [see Warnings and Precautions (5.5)].
- Infections [see Warnings and Precautions (5.6)].
- Hypogammaglobulinemia [see Warnings and Precautions (5.7)].
- Hypersensitivity Reactions [see Warnings and Precautions (5.8)].
- Secondary Malignancies [see Warnings and Precautions (5.9)].

6.1 Clinical Trials Experience

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

The safety data described in this section reflect the exposure of 97 adult patients with relapsed/refractory multiple myeloma in the CARTITUDE-1 study (USA cohort) to ciltaceptagene autoleucel and includes 17 patients (18%) with manufacturing failures either because they received ciltaceptagene autoleucel that did not meet product release specifications or there were insufficient data to confirm product release specifications for CARVYKTI. Patients received ciltaceptagene autoleucel across a dose range of 0.51 to 0.95×10⁶ CAR-positive viable T cells/kg body weight [see Clinical Studies (14)]. Patients with a history of CNS disease (such as seizure or cerebrovascular ischemia) or requiring ongoing treatment with chronic immunosuppression were excluded. The median duration of follow-up was 18 months. The median age of the study population was 61 years (range: 43 to 79). Thirty-nine percent were 65 years old or older, and 59% were men. The Eastern Cooperative Oncology Group (ECOG) performance status at baseline was 0 in 40%, 1 in 56%, and 2 in 4% of patients. Three of the patients treated with ciltaceptagene autoleucel had a creatinine clearance of <45 mL/min at baseline. For the details about the study population, see Clinical Studies (14).

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

The most common (greater or equal to 10%) Grade 3 or higher nonlaboratory adverse reactions were infections-pathogen unspecified (19%), pneumonia (13%), hematologic malignancy (10%) and hypotension (10%). The most common nonlaboratory adverse reactions (incidence greater than or equal to 20%) included pyrexia, cytokine release syndrome, hypogammaglobulinemia, hypotension, musculoskeletal pain, fatigue, infections of unspecified pathogen, cough, chills, diarrhea, nausea, encephalopathy, decreased appetite, upper respiratory tract infection, headache, tachycardia, dizziness, dysphonia, edema, viral infections, coagulopathy, constipation, and vomiting.

Serious adverse reactions occurred in 55% of patients. The most common nonlaboratory (greater than or equal to 5%) serious adverse reactions included CRS (21%), sepsis (7%), encephalopathy (10%), and pneumonia (8%). Fatal adverse reactions occurred in 9% of patients.

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

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

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

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred term</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Coagulopathy¹</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Febrile Neutropenia</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Tachycardia²</td>
<td>27</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea³</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

General disorders and administrative site conditions

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>96</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td>Chills</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>23</td>
<td>0</td>
</tr>
</tbody>
</table>
CARVYKTI® (cilta-cabtagene autoleucel)

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

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred term</th>
<th>Any Grade (%)</th>
<th>Grade 3 or higher (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>95</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Hypergammaglobulinemia</td>
<td>93</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections-pathogen unspecified</td>
<td>41</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>28</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Viral infections</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>48</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>30</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>27</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>23</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Motor dysfunction</td>
<td>16</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>13</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>39</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>15</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Neoplasms benign, malignant, and unspecified (incl cysts and polyps)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic malignancy</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>51</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>19</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>16</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Adverse reactions are reported using MedDRA version 23.0. Carv.STATE includes Activated partial thromboplastin time prolonged, Coagulopathy, Disseminated intravascular coagulation, Hypofibrinogenemia, International normalized ratio increased, and Prothrombin time prolonged. Also includes terms reported under investigation SOC.

Table 4: Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>99</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>98</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>98</td>
</tr>
<tr>
<td>Anemia</td>
<td>72</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>63</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>21</td>
</tr>
</tbody>
</table>

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

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

- Cardiac disorders: cardiac arrhythmias (8%), chest pain (7%)
- Eye disorders: diplopia (1%)
- Gastrointestinal disorders: dysphagia (1%)
- Immune system disorders: hemophagocytic lymphohistiocytosis (1%), hypersensitivity reaction (5%)
- Infections and Infestations: bacterial infections (9%), uritary tract infection (4.1%)
- Injury, Poisoning and procedural complications: fall (3.1%)
- Metabolism and Nutrition disorders: hypothyroidism (1%), pyrexia (1%)
- Vascular Disorders: thrombosis (5%)

Other clinically important adverse reactions that occurred in less than 10% of patients treated with cilta-cabtagene autoleucel include:

- Cardiac arrhythmias includes atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia.
- Chest pain includes Angina pectoris, Chest discomfort, and Chest pain.
- Bacterial infection includes Abscess limb, Cholecytitis, Cholecytitis acute, Clostridium difficile colitis, Clostridium difficile infection, Enterocolitis bacterial, Osteomyelitis, Perirectal abscess, Soft tissue infection, Staphylococcal infection.
- Urinary tract infection includes Urinary tract infection, and Urinary tract infection viral.
- Apheresia includes Aphasias, Dysarthria, and Speech disorder.
- Ataxia includes Ataxia, Balance disorder, and Gait disturbance.
- Peripheral neuropathy includes Peripheral neuropathy, Peripheral motor neuropathy, and Peripheral sensory neuropathy.
- Paresis includes Facial paralysis, and Peroneal nerve palsy.
- Delirium includes Agitation, Hallucination, Irritability, Personality change, and Restlessness.
- Depression includes Depression, and Flat affect.
- Renal failure includes Acute kidney injury, Blood creatinine increased, Chronic kidney disease, and Renal impairment.
- Rash includes Erythema, Rash, Rash maculo-papular, and Rash pustular.
- Thrombosis includes Deep vein thrombosis, and Device related thrombosis.
CARVYKTI® (ciltacabtagene autoleucel)

6.2 Immunogenicity
The immunogenicity of CARVYKTI has been evaluated using a validated assay for the detection of binding antibodies against the extracellular portion of the anti-BCMA CAR pre-dose, and at multiple timepoints post-infusion. In Study CARTITUDE-1, 19 of 97 (19.6%) patients were positive for anti-product antibodies. There was no clear evidence that the observed anti-product antibodies impact CARVYKTI kinetics of initial expansion and persistence, efficacy, or safety.

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on the use of CARVYKTI in pregnant women. No reproductive and development toxicity studies in animals have been conducted with CARVYKTI to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether CARVYKTI has the potential to be transferred to the fetus and cause fetal toxicity. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause fetal toxicity, including B-cell lymphocytopenia and hypogammaglobulinemia. Therefore, CARVYKTI is not recommended for women who are pregnant, or for women of childbearing potential without a prophylactic contraceptive method. Pregnanay testing should be performed in all women of childbearing potential prior to starting treatment with CARVYKTI.

Contraception
There are insufficient data to provide a recommendation concerning duration of contraception following treatment with CARVYKTI. In clinical trials, female patients of childbearing potential were advised to practice a highly effective method of contraception and male patients with partners were pregnant were instructed to use a barrier method of contraception, until one year after the patient has received CARVYKTI infusion. See the prescribing information for lymphodepleting chemotherapy for information on the need for contraception in patients who receive the lymphodepleting chemotherapy.

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

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

8.3 Females and Males of Reproductive Potential
Pregnancy Testing
Pregnancy status for females of child-bearing age should be verified prior to starting treatment with CARVYKTI.

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

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

11 DESCRIPTION
CARVYKTI® (ciltacabtagene autoleucel) is a BCMA-directed genetically modified autologous T cell immunotherapy. CARVYKTI is prepared from the patient’s peripheral blood mononuclear cells, which are obtained via a standard leukapheresis procedure. The mononuclear cells are enriched for T cells and genetically modified ex vivo by transduction with a replication-incompetent lentiviral vector to express a chimeric antigen receptor (CAR) comprising an anti-BCMA targeting domain, which consists of two single-domain antibodies linked to a 4-1BB co-stimulatory domain and a CD3-zeta (CD3ζ) signaling cytoplasmic domain.

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

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

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
CARVYKTI is a BCMA-directed genetically modified autologous T cell immunotherapy, which involves reprogramming a patient’s own T cells with a transgene encoding a chimeric antigen receptor (CAR) that identifies and eliminates cells that express BCMA. The CARVYKTI CAR protein features two BCMA-targeting single-domain antibodies designed to confer high avidity against human BCMA, a 4-1BB co-stimulatory domain and a CD3-zeta (CD3ζ) signaling cytoplasmic domain. Upon binding to BCMA-expressing cells, the CAR promotes T cell activation, expansion, and elimination of target cells.

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

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

Parameter Summary Statistics N=97

<table>
<thead>
<tr>
<th>Parameter Description</th>
<th>Median, range (copies/µg genomic DNA)</th>
<th>Median, range (day)</th>
<th>Median, range (copies* day/µg genomic DNA)</th>
<th>Median, range (day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max}</td>
<td>47806 (7189 - 115234), 97</td>
<td>12.7 (8.7 - 329.8), 97</td>
<td>371569 (58691 - 202412), 97</td>
<td>15.3 (3.0 - 95.4), 42</td>
</tr>
<tr>
<td>t_{max}</td>
<td>12.7 (8.7 - 329.8), 97</td>
<td>371569 (58691 - 202412), 97</td>
<td>15.3 (3.0 - 95.4), 42</td>
<td></td>
</tr>
</tbody>
</table>

After the cell expansion, the persistence phase of ciltacabtagene autoleucel was observed for all patients. At the time of analysis (n=65), the median time for CAR transgene levels in peripheral blood to return to the pre-dose baseline level was approximately 100 days (range: 28 to 365 days) post-infusion. Detectable ciltacabtagene autoleucel exposures in bone marrow indicate a distribution of ciltacabtagene autoleucel from systemic circulation to bone marrow. Similar to blood transgene levels, bone marrow transgene levels declined over time and exhibited high inter-individual variability.

Some patients required tocilizumab, corticosteroids, and anakinra for the management of CRS. Ciltacabtagene autoleucel continues to expand and persist following administration of tocilizumab, corticosteroids, and anakinra. Ciltacabtagene autoleucel median C_{max} and AUC_{0-28d} in patients treated with tocilizumab (n=68) for CRS were 168% and 209% of those in patients (n=29) who did not receive tocilizumab for CRS, respectively. The median C_{max} and AUC_{0-28d} of ciltacabtagene autoleucel in patients who received corticosteroids (n=21) for CRS were 198% and 302% of those patients who did not receive corticosteroids (n=78) for CRS, respectively. In addition, the median C_{max} and AUC_{0-28d} of ciltacabtagene autoleucel in patients who received anakinra (n=18) for CRS were 139% and 232% of those in patients who did not receive anakinra (n=79) for CRS, respectively.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No genotoxicity or carcinogenicity studies have been performed with CARVYKTI as they were not indicated. In vitro studies with CARVYKTI manufactured from healthy donors and patients with multiple myeloma showed no evidence of cytosine independent growth and no preferential integration near genes associated with oncogenic transformation.

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

13.2 Mutagenesis
The efficacy of ciltacabtagene autoleucel was evaluated in CARTITUDE-1, an open-label, single-arm, multicenter trial in adult patients with relapsed or refractory multiple myeloma, who previously received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody (see Adverse Reactions (6.1)).

Patients with known active or prior history of significant central nervous system (CNS) disease, including CNS multiple myeloma, plasma cell leukemia, allogeneic
CARVYKTI® (ciltacabtagene autoleucel)

stem cell transplant within 6 months before apheresis or ongoing treatment with immunosuppressants, creatinine clearance <40 mL/min, absolute lymphocyte concentration <300/L, absolute neutrophil count <750 cells/mm³, platelet count <50,000/mm³, hepatic transaminases >3 times the upper limit of normal, cardiac ejection fraction <45%, or with active serious infection were excluded from the trial.

Of the 113 patients who underwent leukapheresis, 16 patients did not receive ciltacabtagene autoleucel due to progressive disease (n=2), death (n=9), or withdrawal from study (n=5). There were 97 patients in the efficacy evaluable population who received ciltacabtagene autoleucel, including 17 patients (18%) with manufacturing failures either because they received ciltacabtagene autoleucel that did not meet product release specifications for CARVYKTI or received ciltacabtagene autoleucel for which there were insufficient data to confirm product release specifications for CARVYKTI.

Of the 97 efficacy evaluable patients, the median age was 61 years (range: 43 to 78 years), 59% were male, 71% were white, and 18% were black. Most patients (86%) were International Staging System (ISS) Stage I or II. Of the 91 patients for whom baseline cytogenetic data were available, high-risk cytogenetics (presence of 14q14, 14q16, or 17p13 del) were present in 24% of patients. Thirteen percent of the patients had extramedullary disease.

The median number of prior lines of therapy was 6 (range: 3 to 18), with 82% of patients receiving 4 or more prior lines of therapy, 90% of patients had received prior autologous stem cell transplantation (ASCT) and 8% of patients received an allogeneic transplant. Ninety-nine percent of patients were refractory to their last line of prior therapy, and 88% were refractory to a proteasome inhibitor (PI) immunomodulatory agent, and anti-CD38 antibody.

Most patients (75%) treated with ciltacabtagene autoleucel received bridging therapy for control of their multiple myeloma during the manufacturing process. The median time from leukapheresis to product availability was 32 days (range: 27 to 67 days).

The most commonly used agents as bridging therapies (>20% of patients) included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), cyclophosphamide: 22 patients (23%), and pomalidomide: 21 patients (22%). Efficacy was established on the basis of overall response rate, complete response rate and duration of response as assessed by the Independent Review Committee (IRC) using International Myeloma Working Group (IMWG) criteria (see Table 6).

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

The most commonly used agents as bridging therapies included dexamethasone: 62 patients (64%), bortezomib: 26 patients (27%), and pomalidomide: 21 patients (22%).

Table 6: Summary of efficacy results for CARTITUDE-1 based on IRC using IMWG criteria

<table>
<thead>
<tr>
<th>CitcTabtagene autoleucel treated (N=97)</th>
<th>Overall Response Rate (sCR + VGPR) + PRI n (%)</th>
<th>95% CI (%)</th>
<th>Stringent complete response (sCR) n (%)</th>
<th>95% CI (%)</th>
<th>Very good partial response (VGPR) n (%)</th>
<th>95% CI (%)</th>
<th>Partial response (PRI) n (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of responders</td>
<td>95</td>
<td>(92.7, 99.7)</td>
<td>78 (80.4)</td>
<td>(71.1, 87.8)</td>
<td>14 (14.4)</td>
<td>(8.1, 23.0)</td>
<td>3 (3.1)</td>
<td>(0.6, 8.8)</td>
</tr>
<tr>
<td>DOR (Months):Median (95% CI)</td>
<td>NE (23.3, NE)</td>
<td></td>
<td>NE (28.3, NE)</td>
<td></td>
<td>NE (24.4, NE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR if best response is sCR (Months):Median (95% CI)</td>
<td>NE (23.3, NE)</td>
<td></td>
<td>NE (28.3, NE)</td>
<td></td>
<td>NE (24.4, NE)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Notes: Based on a median duration of follow-up of 28 months.

a All complete responses were stringent CRs.

b Exact 95% confidence interval.

c The estimated DOR rate was 60.3% (95% CI: 48.6, 69.5%) at 24 months and 51.2% (95% CI: 39.0, 62.1%) at 30 months.

d Kaplan-Meier estimate.

Table 6: Summary of efficacy results for CARTITUDE-1 based on IRC using IMWG criteria

CARVYKTI® (ciltacabtagene autoleucel)

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

Match the identity of the patient with the patient identifiers on the cassette before receiving the bag.

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

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

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

17 PATIENT COUNSELING INFORMATION

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

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

Advise patients that they will be monitored daily for the first 10 days following the infusion at a REMS-certified healthcare facility, and instruct patients to remain within 15 miles of the facility.

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

Cytokine Release Syndrome (CRS)

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

Neurologic Toxicities

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

Infections

Signs or symptoms associated with infection [see Warnings and Precautions (5.8), Adverse Reactions (6.1)].

Hypersensitivity Reactions

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

Secondary Malignancies

Secondary hematological malignancies, including myelodysplastic syndrome and acute myeloid leukemia, have occurred [see Warnings and Precautions (5.9)].

Advise patients of the need to:

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

Match the identity of the patient with the patient identifiers on the cassette before releasing the bag.

Match the identity of the patient with the patient identifiers on the cassette before releasing the bag.

Manufactured/Marketed by:

Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

Marketed by:

Legend Biotech
Somerset, NJ 08873, USA

For patient information: www.janssenpatents.com
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MEDICATION GUIDE
CARVYKTI® (car-vick-tee)
ciltacabtagene autoleucel

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

What is the most important information I should know about CARVYKTI?
CARVYKTI may cause side effects that are severe or life-threatening and can lead to death. Call your healthcare provider or get emergency help right away if you get any of the following:
- fever (100.4°F/38°C or higher)
- chills or shaking chills
- fast or irregular heartbeat
- difficulty breathing
- very low blood pressure
- dizziness/light headedness
- effects on your nervous system, some of which can occur days or weeks after you receive the infusion, and may initially be subtle such as:
  - feeling confused, less alert, or disoriented, having difficulty speaking or slurred speech, having difficulty reading, writing, and understanding words, memory loss
  - loss of coordination affecting movement and balance, slower movements, changes in handwriting
  - personality changes including a reduced ability to express emotions, being less talkative, disinterest in activities, and reduced facial expression
  - tingling, numbness, and pain of hands and feet, difficulty walking, leg and/or arm weakness, and difficulty breathing
  - facial numbness, difficulty moving muscles of face and eyes

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

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

Before you receive CARVYKTI tell your healthcare provider about all your medical conditions, including if you have:
- Current or past neurologic problems (such as seizures, stroke, new or worsening memory loss)
- Lung or breathing problems
- Heart problems
- Liver problems
- Kidney problems
- A recent or active infection
- Low blood counts

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

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

Before you get CARVYKTI, your healthcare provider will give you chemotherapy for 3 days to prepare your body. 30 to 60 minutes before you are given CARVYKTI, you may be given other medicines. These may include:
- medicines for an allergic reaction (anti-histamines)
- medicines for fever (such as acetaminophen)

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

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

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

Your healthcare provider will want to do blood tests to follow your progress. It is important that you have your blood tested. If you miss an appointment, call your healthcare provider as soon as possible to reschedule.
**What should I avoid after receiving CARVYKTI?**
- Do not drive, or operate heavy machinery, or do other activities that could be dangerous if you are not mentally alert, for at least 8 weeks after you get CARVYKTI. This is because the treatment can cause memory and coordination problems, sleepiness, confusion, dizziness, seizures, or other neurologic side effects as discussed by your healthcare provider.
- You must not be given certain vaccines called live vaccines for some time before and after CARVYKTI treatment. Talk to your healthcare provider if you need to have any vaccinations.
- Do not donate blood, organs, tissues, or cells for transplantation.

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

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

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

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

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

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

CARVYKTI can increase your risk of getting cancers including certain types of blood cancers. Your healthcare provider should monitor you for this.

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

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

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

**General information about the safe and effective use of CARVYKTI**

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

**What are the ingredients in CARVYKTI?**

**Active ingredient:** ciltacabtagene autoleucel

**Inactive ingredients:** DMSO

Manufactured/Marketed by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License Number 1884

Marketed by: Legend Biotech, Somerset, NJ 08873, USA. For patent information: www.janssenpatents.com

For more information, call 1-800-526-7736 or go to www.CARVYKTI.com.

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

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