Risk Evaluation and Mitigation Strategy (REMS) Document
CARVYKTI™ (ciltaacabtagene autoleucel) REMS Program

I. Administrative Information

Application Number: BLA 125746
Application Holder: Janssen Biotech, Inc.
Initial REMS Approval: 02/2022

II. REMS Goals

The goals of the CARVYKTI REMS are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

1. Ensuring that hospitals and their associated clinics that dispense CARVYKTI are specially certified and have on-site, immediate access to tocilizumab.

2. Ensuring that those who prescribe, dispense, or administer CARVYKTI are aware of how to manage the risks of CRS and neurological toxicities.

III. REMS Requirements

Janssen Biotech, Inc. must ensure that hospitals and their associated clinics, and patients comply with the following requirements:

1. Hospitals and their associated clinics that dispense CARVYKTI must:

   To become certified to dispense

   1. Have a minimum two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).

   2. Designate an Authorized Representative to carry out the certification process and oversee implementation and compliance with the REMS Program requirements on behalf of the hospital and associated clinic(s).

   3. Have the authorized representative complete the Training Program and Adverse Reaction Management Guide provided by the REMS Program.

   4. Have the Authorized Representative successfully complete the Knowledge Assessment and submit it to the REMS Program.

   5. Have the Authorized Representative enroll in the REMS Program by completing the Hospital Enrollment Form and submitting it to the REMS Program.

   6. Train all relevant staff involved in prescribing, dispensing, or administering of CARVYKTI on the REMS Program requirements using the Training Program and the Adverse Reaction Management Guide.

   7. Have all relevant staff involved in prescribing, dispensing, or administering of CARVYKTI successfully complete the Knowledge Assessment and submit it to the REMS Program.
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<table>
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<tbody>
<tr>
<td>8.</td>
<td>Establish processes and procedures to ensure relevant new staff involved in the prescribing, dispensing, or administration of CARVYKTI are trained and complete the Knowledge Assessment and submit it to the REMS Program.</td>
</tr>
<tr>
<td>9.</td>
<td>Establish processes and procedures to verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).</td>
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<tr>
<td>10.</td>
<td>Establish processes and procedures to provide patients with the Patient Wallet Card.</td>
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<tr>
<td><strong>Before infusion</strong></td>
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<tr>
<td>11.</td>
<td>Verify that a minimum of two doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours) through the processes and procedures established as a requirement of the REMS Program.</td>
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<tr>
<td><strong>Before discharge</strong></td>
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<td>12.</td>
<td>Provide the patient with the Patient Wallet Card through the processes and procedures established as a requirement of the REMS Program.</td>
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<tr>
<td><strong>To maintain certification to dispense if there is a change in the authorized representative</strong></td>
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<td>13.</td>
<td>Have a new Authorized Representative enroll in the REMS Program by completing the Hospital Enrollment Form.</td>
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<td><strong>To maintain certification to dispense, if CARVYKTI has not been infused at least once annually from the date of certification in the REMS Program</strong></td>
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<td>14.</td>
<td>Train all relevant staff involved in prescribing, dispensing, or administering of CARVYKTI on the REMS Program requirements using the Training Program and the Adverse Reaction Management Guide.</td>
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<tr>
<td>15.</td>
<td>Have all relevant staff involved in prescribing, dispensing, or administering CARVYKTI successfully complete the Knowledge Assessment.</td>
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<td><strong>At all times</strong></td>
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<td>16.</td>
<td>Report any serious' adverse events suggestive of CRS or neurological toxicities to the REMS Program.</td>
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<td>17.</td>
<td>Maintain records of staff training.</td>
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<td>18.</td>
<td>Maintain records that processes and procedures are in place and are being followed.</td>
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<td>19.</td>
<td>Comply with audits carried out by Janssen Biotech, Inc. or a third party acting on behalf of Janssen Biotech, Inc. to ensure that all training, processes, and procedures are in place and are being followed.</td>
</tr>
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</table>
2. Patients who are prescribed CARVYKTI:

Before discharge

1. Receive the Patient Wallet Card.

Janssen Biotech, Inc. must provide training to relevant staff who prescribe, dispense, or administer CARVYKTI.

The training includes the following educational materials: Training Program, Adverse Reaction Management Guide, and Knowledge Assessment. The training must be provided in-person, via live webcast, or online.

To support REMS Program operations, Janssen Biotech, Inc. must:

1. Ensure CARVYKTI is distributed only to certified hospitals or their associated clinics.
2. Establish and maintain the REMS Program Website, www.CARVYKTIREMS.com. The REMS Program Website must include the capability to enroll, complete training online, maintain records of that training, and option to print the Prescribing Information (PI), Medication Guide, and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program Website.
3. Make the REMS Program website fully operational and all REMS materials available through website and the REMS Program Coordinating Center.
4. Establish and maintain a REMS Program Coordinating Center for REMS participants at 1-844-672-0067.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or have been certified in the REMS Program.
6. Ensure hospitals and their associated clinics are able to enroll in the REMS Program online, through fax and by e-mail.
7. Notify hospitals and their associated clinics within 7 calendar days after they become certified in the REMS Program.

To ensure REMS participants’ compliance with the REMS Program, Janssen Biotech, Inc. must:

8. Verify annually that the designated authorized representative for certified hospitals and their associated clinics remains the same. If different, the hospital and their associated clinics must re-certify with a new authorized representative.
9. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: CARVYKTI distribution and dispensing; certification of hospitals and their associated clinics, and audits of REMS participants. These records must be readily available for FDA inspections.
10. Monitor hospitals and their associated clinics on an ongoing basis to ensure the requirements of the REMS are being met. Take corrective action if non-compliance is identified, including de-certification.
11. Maintain an ongoing annual audit plan of hospitals and their associated clinics.
12. Audit all certified hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of CARVYKTI to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements. Certified hospitals and their associated clinics must also be included in Janssen Biotech, Inc.’s ongoing annual audit plan.
13. Take reasonable steps to improve implementation of and compliance with the requirements in the CARVYKTI REMS Program based on monitoring and evaluation of the CARVYKTI REMS Program.

IV. REMS Assessment Timetable

Janssen Biotech, Inc. must submit REMS Assessments to the FDA at 6 months, 12 months, and annually thereafter from the date of the initial approval of the REMS (02/2022). To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 calendar days before the submission date for that assessment. Janssen Biotech, Inc. must submit each assessment so that it will be received by the FDA on or before the due date.

V. REMS Materials

The following materials are part of the CARVYKTI REMS:

**Enrollment Forms**

Healthcare Facility:

1. Hospital Enrollment Form

**Training and Educational Materials**

Patient:

2. Patient Wallet Card

Healthcare setting:

3. Training Program
4. Adverse Reaction Management Guide
5. Knowledge Assessment

**Other Materials**

6. REMS Program Website

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1 For the purpose of this REMS, serious adverse event is 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.
CARVYKTI™ RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Hospital Enrollment Form

Phone: 1-844-672-0067
Fax: 1-877-778-3865
E-mail: CARVYKTI@JanssenREMS.com
www.CARVYKTIREMS.com

Instructions

CARVYKTI™ (ciltaecabtagene autoleucel) is only available through the CARVYKTI Risk Evaluation and Mitigation Strategy (REMS).

In order to dispense CARVYKTI, Hospitals and their Associated Clinics must be certified in the CARVYKTI REMS and have on-site immediate access to tocilizumab (the “Hospitals and their Associated Clinics”). Hospitals and their Associated Clinics must designate an Authorized Representative to:

• Complete the certification process by completing the Hospital Enrollment Form on behalf of the Hospital and Associated Clinics.
• Oversee implementation and compliance with the CARVYKTI REMS requirements as outlined below.

To comply:

• Please complete all required fields below and submit this enrollment form to the REMS Coordinating Center via fax to 1-877-778-3865, e-mail at CARVYKTI@JanssenREMS.com or complete it online at www.CARVYKTIREMS.com. You will receive a confirmation via e-mail.
• Completion of this form does not guarantee your Hospital and Associated Clinics will be certified to administer CARVYKTI.
• The CARVYKTI REMS will assess and provide confirmation of certification via e-mail after processing this enrollment form and a successfully completed Knowledge Assessment.
• Product orders cannot be placed until the Hospital and Associated Clinics certification is complete.

If you have any questions, require additional information, or need further copies of any of the CARVYKTI REMS materials, please visit the REMS website at www.CARVYKTIREMS.com or call the CARVYKTI REMS Coordinating Center at 1-844-672-0067.

Hospitals and Associated Clinics Information (All Fields Required)

☐ New Certification  ☐ Change in Authorized Representative

Hospital and Associated Clinics Name:

Hospital and Associated Clinics REMS ID:

Address:

City: ______________________  State: ______________________  Zip Code: ______________________

Phone: (___) ___-______  Fax: (___) ___-______

Authorized Representative Information (All Fields Required)

First Name: ______________________  Last Name: ______________________

Credentials:  ☐ DO  ☐ MD  ☐ R.Ph  ☐ NP/PA  ☐ Other (please specify) ______________________

Phone: (___) ___-______  Fax: (___) ___-______  e-mail: ______________________

Authorized Representative Signature ______________________  Date (MM/DD/YYYY) ______________________
Authorized Representative Responsibilities

On behalf of my Hospital and Associated Clinics, I am the Authorized Representative, designated by my Hospital and Associated Clinics, to oversee implementation and coordinate the activities of the CARVYKTI REMS. By signing this form, I agree, on behalf of myself and my Hospital and Associated Clinics, to comply with all REMS Requirements. I will:

- Complete the Training Program, Adverse Reaction Management Guide, Knowledge Assessment, and the Hospital Enrollment Form.
  - Submit the completed Knowledge Assessment and the Hospital Enrollment Form to the REMS Coordinating Center via fax to 1-877-778-3865, e-mail at CARVYKTI@JanssenREMS.com, or complete it online at www.CARVYKTIREMS.com.
  - Oversee implementation and compliance with the CARVYKTI REMS.
- Ensure that my Hospital and Associated Clinics establishes processes and procedures that are subject to monitoring by Janssen Biotech, Inc, or a third party acting on behalf of Janssen Biotech, Inc to ensure compliance with the requirements of the CARVYKTI REMS, including the following, before administering CARVYKTI:
  a. Ensuring all relevant staff involved in the prescribing, dispensing, or administering of CARVYKTI are trained on the REMS requirements and successfully complete the Knowledge Assessment.
  b. Performing re-education of all staff involved in the prescribing, dispensing, or administering of CARVYKTI on the REMS requirements using the Training Program and having staff successfully complete the Knowledge Assessment, if CARVYKTI has not been infused at least once annually from the date of initial certification of the Hospital and Associated Clinics in the CARVYKTI REMS.
  c. Prior to dispensing CARVYKTI, put processes and procedures in place to verify on-site, immediate access to at least two doses of tocilizumab for each patient, for administration within two hours after infusion.
  d. Before discharge, provide patients or their caregivers with the Patient Wallet Card through the processes and procedures established as a requirement of the REMS program and instruct them to remain close to the location where treatment was received for at least 4 weeks following infusion.

As a condition of certification, the Hospital and Associated Clinics shall:

- Ensure that if the Hospital and Associated Clinics designate a new Authorized Representative, the new Authorized Representative must review the Training Program, the Adverse Reaction Management Guide, complete the Knowledge Assessment, complete a new Hospital Enrollment Form and submit the forms via fax to 1-877-778-3865, e-mail at CARVYKTI@JanssenREMS.com or complete it online at www.CARVYKTIREMS.com.
- Report any serious adverse events suggestive of cytokine release syndrome or neurological toxicities.
- Dispense CARVYKTI to patients only after verifying on-site, immediate access to at least two doses of tocilizumab for each patient, for administration within 2 hours after infusion.
- Maintain documentation of all processes and procedures for the CARVYKTI REMS and provide documentation upon request by Janssen Biotech, Inc or third party acting on behalf of Janssen Biotech, Inc.
- Comply with audits by Janssen Biotech, Inc, or a third party acting on behalf of Janssen Biotech, Inc.
IMPORTANT SAFETY INFORMATION FOR PATIENTS RECEIVING TREATMENT WITH CARVYKTI

This patient has received CARVYKTI.

For Healthcare Professionals

Carry this card with you at all times. SHOW THIS CARD to any healthcare professional involved in your care and if you go to the emergency room.

IMPORTANT SAFETY INFORMATION FOR PATIENTS RECEIVING TREATMENT WITH CARVYKTI
FOR THE PATIENT

Call your healthcare professional or get emergency help right away if you recognize any of these symptoms:

- Leg and arm weakness with paralysis
- Fever (100.4°F or 38°C or higher)
- Chills or shaking chills
- Difficulty breathing
- Fast or irregular heartbeat
- Very low blood pressure
- Dizziness or light-headedness
- Muscle or joint pain
- Confusion or disorientation
- Difficulty speaking, reading, or writing
- Changes in balance or coordination
- Difficulty moving muscles of face and eyes
- Facial numbness

- Tingling, numbness, and pain of hands and feet
- Slower movements
- Shuffling feet or small steps when walking
- Personality changes (e.g., less talkative, disinterest in activities)
- Smiling, frowning, or showing emotion less
- Difficulty performing simple tasks (e.g., getting dressed, feeding oneself)
- Memory loss or fogginess
- Smaller handwriting
- Tremor

You should always ask your doctor about taking other medications while taking CARVYKTI.

IMPORTANT TO REMEMBER: Stay close to the location where you received your CARVYKTI infusion for at least 4 weeks. If you have any of these symptoms call your doctor or seek emergency medical attention right away! These are not all of the possible side effects of CARVYKTI. Tell your doctor if you have any side effect that bothers you or does not go away.
CARVYKTI™ Risk Evaluation and Mitigation Strategy (REMS)
CARVYKTI Training Module

- This educational module contains information on adverse reactions associated with CARVYKTI, including cytokine release syndrome and neurological toxicities. These are not all the adverse reactions associated with CARVYKTI.
What is a REMS?

- A Risk Evaluation and Mitigation Strategy (REMS) is a program required by the FDA to manage known or potential serious risks associated with a drug product. The FDA has determined that a REMS is necessary to ensure that the benefits of CARVYKTI outweigh its risks.

- The purpose of the CARVYKTI REMS is to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities.
CARVYKTI Indication

- CARVYKTI is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.
CARVYKTI REMS Goal

The goal of the CARVYKTI REMS is to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that Hospitals and their Associated Clinics that dispense CARVYKTI are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring those who prescribe, dispense, or administer CARVYKTI are aware of how to manage the risks of CRS and neurological toxicities.
# CARVYKTI REMS Tools

| **Hospital Enrollment Form** | • Completed by Authorized Representative  
  • Online, e-mail, fax |
|-----------------------------|------------------------------------------------|
| **Training Program**        | • Educates on the key risks and management of CRS and neurological toxicities  
  • CARVYKTI REMS Overview |
| **Knowledge Assessment**    | • Fortifies the key risk messages about CRS and neurological toxicities  
  • Multiple choice questions |
| **Adverse Reaction Management Guide** | • Supplemental guidance for the CARVYKTI USPI |
| **Patient Wallet Card**     | • Patients are to always carry wallet card after infusion  
  • Reminder of signs and symptoms requiring immediate medical attention  
  • Instructions to remain close to the location where treatment was received for at least 4 weeks following infusion |
| **REMS Website**            | • Dedicated resource for REMS information and program enrollment |
Hospital and Associated Clinics Certification Requirements

To become certified to dispense CARVYKTI the Hospital and Associated Clinics must:

- Designate an Authorized Representative to complete the certification process and oversee implementation and compliance with the CARVYKTI REMS on behalf of the Hospital and Associated Clinics
- Have the Authorized Representative enroll in the REMS program by completing the **Hospital Enrollment Form** and submitting it to the REMS program
- Have on-site, immediate access to at least two doses of tocilizumab for each patient, for administration within two hours after infusion
- Train all relevant staff involved in prescribing, dispensing, or administering CARVYKTI on the REMS requirements using this **Training Program** and the **Adverse Reaction Management Guide** and successfully complete the **Knowledge Assessment**
- Have the Authorized Representative review this **Training Program**, the **Adverse Reaction Management Guide**, and successfully complete and submit the **Knowledge Assessment** to the REMS program
Hospital and Associated Clinics Certification Requirements

Establish and maintain processes and procedures to:

- Ensure new staff involved in the prescribing, dispensing, or administration of CARVYKTI are trained and complete the *Knowledge Assessment*
- Verify prior to infusion, that there is on-site, immediate access to at least two doses of tocilizumab for each patient, for administration within two hours after infusion
- Provide patients or their caregivers with the *Patient Wallet Card* before discharge through the processes and procedures established as a requirement of the REMS program
Hospital and Associated Clinics Certification Requirements

To maintain certification to dispense:

• Any new Authorized Representative must enroll in the REMS program by completing the Hospital Enrollment Form

If CARVYKTI has not been infused at least once annually from the date of certification in the CARVYKTI REMS:

• Perform re-education of all staff involved in prescribing, dispensing, or administering of CARVYKTI on the REMS program requirements using this Training Program, Adverse Reaction Management Guide, and successfully complete the Knowledge Assessment

At all times

• Report any serious adverse events* including those suggestive of CRS or neurological toxicities to the REMS program
• Maintain records of staff training
• Maintain records that all processes and procedures are in place and are being followed
• Comply with audits carried out by Janssen Biotech, Inc or a third party acting on behalf of Janssen Biotech, Inc to ensure that all REMS specific processes and procedures are in place and being followed

*A serious AE is when a patient’s outcome is: Death, Life-threatening, Hospitalization (initial or prolonged), Disability or Permanent Damage
Who Can Be an Authorized Representative?

An Authorized Representative at the Hospital and Associated Clinics can be a:

- Physician
- Nurse
- Any responsible individual assigned by the Hospital and Associated Clinics

One Authorized Representative must enroll for each Hospital and Associated Clinics and uphold the REMS requirements as stated on the Hospital Enrollment Form.
Cytokine Release Syndrome (CRS) and Neurological Toxicities
CARVYKTI 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.

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 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.

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

- CRS, including fatal or life-threatening reactions, occurred following treatment with CARVYKTI. In Study 68284528MMY2001 (referred to as CARTITUDE-1) CRS was graded using ASTCT 2019 criteria which is different from the 2014 Lee criteria. Specifically, organ toxicity associated with CRS is not captured by 2019 ASTCT criteria; only fever, hypoxia and hypotension are considered for grading

- CARTITUDE-1 (n=97), CRS was reported in the majority 95% (92/97) of patients
  - Grade 1/2: 90% (n=87)
  - Grade 3/4: 4% (n=4)
  - Grade 5: 1% (n=1)

- The median time to onset of CRS was 7 days (range of 1 to 12 days)
- Median duration of CRS was 4 days (range of 1 to 40 days) for all but one patient who had a duration of 97 days complicated by secondary hemophagocytic lymphohistiocytosis (HLH) with a subsequent fatal outcome
# CARTITUDE-1 Management of CRS

## Patients with CRS in All Treated Analysis Set (n=97)

69 (71%) of patients received tocilizumab and/or anakinra and/or corticosteroids

- 68 patients received tocilizumab, of which 49 (72%) received a single dose (with or without anakinra and/or corticosteroids)
- 24 (25%) patients received tocilizumab and corticosteroids (with or without anakinra)
- 18 (18.6%) patients received tocilizumab and anakinra (with or without corticosteroids)
- 1 patient received corticosteroids only and no patients received anakinra only

<table>
<thead>
<tr>
<th>Max CRS Grade</th>
<th>None²</th>
<th>Tocilizumab alone</th>
<th>Corticosteroids alone</th>
<th>Tocilizumab AND corticosteroids</th>
<th>Tocilizumab AND anakinra</th>
<th>Tocilizumab AND corticosteroids AND anakinra</th>
<th>Total CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21 (22%)</td>
<td>19 (20%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
<td>4 (4%)</td>
<td>49 (51%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (2%)</td>
<td>20 (21%)</td>
<td>-</td>
<td>8 (8%)</td>
<td>1 (1%)</td>
<td>7 (7%)</td>
<td>38 (39%)</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>1 (1%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 (2%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
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<td>1 (1%)</td>
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<td>1 (1%)</td>
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<tr>
<td>5</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>23 (24%)</td>
<td>40 (41%)</td>
<td>1 (1%)</td>
<td>10 (10%)</td>
<td>4 (4%)</td>
<td>14 (14%)</td>
<td>92 (95%)</td>
</tr>
</tbody>
</table>

1. Grading by American Society for Transplantation and Cellular Therapy (ASTCT) CRS grading criteria
2. Other symptomatic treatments (e.g., analgesics/anti-inflammatory medications) not shown
Clinical Signs and Symptoms of CRS

- Patients should be closely monitored for signs or symptoms of CRS, including fever
- Organ toxicity may occur or persist after resolution of fever, hypotension and hypoxia
- Potentially life-threatening complications of CRS may include:
  - cardiac dysfunction
  - HLH

**Signs and Symptoms**

- Fever (with or without rigors)
- Chills
- Hypoxia
- Elevated liver enzymes
- Dyspnea
- Hypotension
- Arthralgia
- Nausea
- Vomiting
- Tachycardia
- Headache
- Kidney injury
- Pulmonary edema
- Capillary leak
Risk Factors for Severe CRS

According to literature reports, the severity of CRS has been related to:

- High pre-infusion tumor burden¹,²,³,⁴
- Active infection⁴,⁵ and early onset of fever⁵,⁶
- Persistent fever after symptomatic treatment⁶,⁷

*For patients experiencing ANY of the above, early use (Grade 1 CRS) of tocilizumab may be considered. Refer to the CARVYKTI REMS Adverse Reaction Management Guide for additional information (see Slide 18).

Preparing the Patient for CARVYKTI Infusion

• Confirm availability of CARVYKTI prior to starting the lymphodepleting chemotherapy regimen
• Ensure that a minimum of two doses of tocilizumab are available prior to infusion of CARVYKTI
• Administer the lymphodepleting chemotherapy regimen: cyclophosphamide 300 mg/m² intravenously (IV) and fludarabine 30 mg/m² IV daily for 3 days
• Lymphodepleting regimen must be delayed if a patient has serious adverse reactions from preceding bridging therapies (including clinically significant active infection, cardiac toxicity, and pulmonary toxicity) or active graft versus host disease in 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
• Delay the infusion of CARVYKTI if the patient has:
  − 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
CRS Management

- Identify CRS based on clinical presentation and institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids.

- Consider laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

- 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.

- 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.

- 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-TNFα, anti-T cell therapies).

Refer to the CARVKTI REMS Adverse Reaction Management Guide for additional information.
# CRS Management Guidance

## CRS Grade

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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 | 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 canulae or blow-by, or, | 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.  
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 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. | Consider dexamethasone 10 mg IV every 12-24 hours. |

---

*Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity.

**Refer to tocilizumab prescribing information for details.

*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.

Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.

Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days.

Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
**CRS Management Guidance**

**Table 1: CRS Management Guidance**

<table>
<thead>
<tr>
<th>Presenting Symptoms</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3</strong>&lt;br&gt;Symptoms require and respond to aggressive intervention.&lt;br&gt;Temperature ≥38°C (100.4°F) with:&lt;br&gt;Hypotension requiring one vasopressor with or without vasopressin, and/or,&lt;br&gt;Hypoxia requiring oxygen via high-flow nasal canulae, facemask, non-rebreather mask, or Venturi mask, or,&lt;br&gt;Grade 3 organ toxicity or Grade 4 transaminitis.</td>
<td>Per Grade 2&lt;br&gt;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).&lt;br&gt;If no improvement within 24 hours or continued rapid progression, switch to methylprednisolone 2 mg/kg IV every 12 hours.&lt;br&gt;After 2 doses of tocilizumab, consider alternative anti-cytokine agents.&lt;br&gt;Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.</td>
<td>Administer dexamethasone 10 mg IV every 12 hours.</td>
</tr>
<tr>
<td><strong>Grade 4</strong>&lt;br&gt;Life-threatening symptoms.&lt;br&gt;Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD). Temperature ≥38°C (100.4°F) with:&lt;br&gt;Hypotension requiring multiple vasopressors (excluding vasopressin), and/or,&lt;br&gt;Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation), or,&lt;br&gt;Grade 4 organ toxicity (excluding transaminitis).</td>
<td>Per Grade 2&lt;br&gt;Administer Dexamethasone 20 mg IV every 6 hours.&lt;br&gt;After 2 doses of tocilizumab, consider alternative anti-cytokine agents.&lt;br&gt;Do not exceed 3 doses of tocilizumab in 24 hours, or 4 doses in total.&lt;br&gt;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 (e.g., other anti-T cell therapies).</td>
<td></td>
</tr>
</tbody>
</table>

---

* Based on ASCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity.<br>† Refer to tocilizumab prescribing information for details.<br>‡ 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.<br>§ Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.<br>¶ Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.<br>∥ Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days.<br>∥ Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
Neurological Toxicities

- Neurologic toxicities, which may be severe, life-threatening, or fatal, occurred following treatment with CARVYKTI. Neurologic toxicities include:
  - Immune Cell-Associated Neurologic Syndrome (ICANS) (see Slide 21)
  - Parkinsonism (see slide 22)
  - Peripheral neuropathy (see Slide 28)
  - Guillain-Barré Syndrome (GBS) (see Slide 30)
  - Cranial nerve palsies (see Slide 31)

- In CARTITUDE-1 (n=97), one or more subtype of neurological toxicity occurred in 26% of patients with 10 (10.3%) being Grade 3/4 and 1 (1%) Grade 5.

- 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
Neurological Toxicities - ICANS

- ICANS occurred in 23% of patients (n=22) with 3% (n=3) experiencing Grade 3 or 4 events and Grade 5 events in 2% of patients.
  - Symptoms included:
    - Aphasia
    - Slow speech
    - Dysgraphia
    - Encephalopathy
    - Depressed level of consciousness
    - Confusional state
- Median time from infusion to first onset of ICANS was 8 days (range of 1 to 28 days) and median duration was 7.5 days (range of 2 to 927 days).
- ICANS did not resolve in one patient and was ongoing at death.

In Study 68284528MMY2001 (referred to as CARTITUDE-1) 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
Parkinsonism

- 5% (5 patients, all male) from CARTITUDE-1, experienced signs and symptoms of Parkinsonism distinct from ICANS
  - Some symptoms may be subtle (e.g., flat affect, fatigue, falling asleep easily)
  - Given the serious nature of this toxicity, 3 of the 5 patients could not work or care for themselves

- Adverse reactions included:
  - Movement (e.g., micrographia, tremors)
  - Cognitive (e.g., memory loss, disturbances in attention)
  - Personality change (e.g., reduced facial expression, flat affect)

- The median time to first symptom onset was 43 days (range of 15 to 108 days)
  - One patient died due to this toxicity
  - One patient had Grade 2 toxicity and 1 patient had Grade 4 toxicity ongoing at death, due to infectious causes
  - One patient with Grade 1 toxicity and 1 patient with Grade 2 toxicity had ongoing symptoms at last visit

- All 5 patients had a history of prior CRS (n=4 Grade 2; n=1 Grade 3), while 4 of 5 patients had prior ICANS (n=3 Grade 1; n=1 Grade 2)

- Treatment with levodopa/carbidopa (n=2), was not effective in improving symptomatology in these patients

- One additional Parkinsonism case occurred after treatment with ciltacabtagene autoleucel in another ongoing study
## Signs and Symptoms of Parkinsonism

<table>
<thead>
<tr>
<th>Movement Disorder</th>
<th>Cognitive Impairment</th>
<th>Personality Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bradykinesia</td>
<td>• Depressed level of consciousness*</td>
<td>• Flat affect</td>
</tr>
<tr>
<td>• Cogwheel rigidity</td>
<td>• Memory impairment</td>
<td>• Personality change</td>
</tr>
<tr>
<td>• Dysgraphia</td>
<td>• Mental status changes</td>
<td>• Reduced facial expression</td>
</tr>
<tr>
<td>• Gait disturbance</td>
<td>• Psychomotor retardation</td>
<td>• Apathy</td>
</tr>
<tr>
<td>• Micrographia</td>
<td>• Apraxia</td>
<td>• Monotone speech</td>
</tr>
<tr>
<td>• Motor dysfunction, Parkinsonism</td>
<td>• Akinetic mutism</td>
<td>• Low (volume) speech</td>
</tr>
<tr>
<td>• Posture abnormal, Stereotypy</td>
<td>• Mental status changes</td>
<td>• Withdrawn</td>
</tr>
<tr>
<td>• Tremor*</td>
<td>• Wordfinding difficulties</td>
<td>• Decreased personal hygiene</td>
</tr>
<tr>
<td>• Decreased arm swing</td>
<td>• Intermittent confusion</td>
<td></td>
</tr>
<tr>
<td>• Involuntary movements of head</td>
<td>• Confusional state</td>
<td></td>
</tr>
<tr>
<td>• Difficulty motor planning</td>
<td>• Altered mentation</td>
<td></td>
</tr>
<tr>
<td>• Saccadic eye movements</td>
<td>• Bradylalia</td>
<td></td>
</tr>
<tr>
<td>• Decreased eye blink</td>
<td>• Abnormal glabellar reflex</td>
<td></td>
</tr>
<tr>
<td>• Tongue fasciculations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Persistence of tongue protrusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Masked facies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Symptoms seen both during ICANS and later during Parkinsonism*
## Prior CRS/ICANS (Grade), Interventions Used and Outcomes of Parkinsonism Cases

<table>
<thead>
<tr>
<th>Study Number and Patient</th>
<th>Prior CRS Y/N (Max Grade)</th>
<th>Prior ICANS Y/N (Max Grade)</th>
<th>Maximum toxicity Grade of Parkinsonism</th>
<th>Interventions Used</th>
<th>Outcome of Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTITUDE-1: Patient 1</td>
<td>Y (3)</td>
<td>N</td>
<td>2</td>
<td>anakinra, carbidopa-levodopa, cyclophosphamide, IT cytarabine, hydrocortisone, IVIG, plasmapheresis</td>
<td>Not improved by time of death*</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 2</td>
<td>Y (2)</td>
<td>Y (1)</td>
<td>5</td>
<td>cyclophosphamide, dexamethasone</td>
<td>Death</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 3</td>
<td>Y (2)</td>
<td>Y (1)</td>
<td>3</td>
<td>cyclophosphamide, dexamethasone, IT methotrexate, hydrocortisone, alprazolam</td>
<td>Improving</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 4</td>
<td>Y (4)</td>
<td>Y (1)</td>
<td>3</td>
<td>None reported</td>
<td>Improving</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 5</td>
<td>Y (2)</td>
<td>Y (2)</td>
<td>4</td>
<td>anakinra, carbidopa-levodopa, cyclophosphamide, IT cytarabine, dasatinib, dexamethasone, hydrocortisone, levetiracetam, IT methotrexate, siltuximab</td>
<td>Not improved by time of death*</td>
</tr>
</tbody>
</table>

IT = intrathecal  
IVIG = Intravenous Immunoglobulin  
* = Due to other causes
Neurological Toxicities Management

- Monitor patients for signs or symptoms of ICANS for 4 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 (refer to the *Adverse Reaction Management Guide*)
- Rule out other causes of neurological symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurological toxicities
## Neurological Toxicities Management Guide

### Table 2: Guidelines for the Management of ICANS

<table>
<thead>
<tr>
<th>ICANS Grade&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt;ICE score-7-9&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;or depressed level of consciousness: awakens spontaneously.</td>
<td>Consider dexamethasone&lt;sup&gt;c&lt;/sup&gt; 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><strong>Grade 2</strong>&lt;br&gt;ICE score-3-6&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;or depressed level of consciousness: awakens to voice.</td>
<td>Administer dexamethasone&lt;sup&gt;c&lt;/sup&gt; 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. 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 (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td><strong>Grade 3</strong>&lt;br&gt;ICE score-0-2&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;(If ICE score is 0, but the patient is arousable (e.g., awake with global aphasia) and able to perform assessment)&lt;br&gt;or depressed level of consciousness: awakens only to tactile stimulus,&lt;br&gt;or seizures, either:&lt;br&gt;• any clinical seizure, focal or generalized, that resolves rapidly, or&lt;br&gt;• non-convulsive seizures on EEG that resolve with intervention,&lt;br&gt;or raised intracranial pressure (ICP): focal/local edema on neuroimaging&lt;sup&gt;d&lt;/sup&gt;.</td>
<td>Administer dexamethasone&lt;sup&gt;c&lt;/sup&gt; 10 mg-20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate dexamethasone&lt;sup&gt;c&lt;/sup&gt; 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. 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).</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity.

<sup>b</sup> 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.

<sup>c</sup> All references to dexamethasone administration are dexamethasone or equivalent.

<sup>d</sup> 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 CTCA v5.0.
<table>
<thead>
<tr>
<th>ICANS Grade &lt;sup&gt;a&lt;/sup&gt;</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4</td>
<td></td>
</tr>
<tr>
<td>ICE score = 0&lt;sup&gt;b&lt;/sup&gt; (Patient is unarousable and unable to perform ICE assessment)</td>
<td>Administer dexamethasone &lt;sup&gt;c&lt;/sup&gt; 20mg IV every 6 hours.</td>
</tr>
<tr>
<td>or depressed level of consciousness either:</td>
<td>If no improvement after 24 hours or worsening of neurologic toxicity, escalate to high-dose methylprednisolone (1-2g/day, repeated every 24 hours if needed; taper as clinically indicated).</td>
</tr>
<tr>
<td>• patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or</td>
<td>Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td>• stupor or coma,</td>
<td>If raised ICP/cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1-2g/day, repeat every 24 hours if needed; taper as clinically indicated), and consider neurology and/or neurosurgery consultation.</td>
</tr>
<tr>
<td>or seizures, either:</td>
<td></td>
</tr>
<tr>
<td>• life-threatening prolonged seizure (&gt;5min), or</td>
<td></td>
</tr>
<tr>
<td>• repetitive clinical or electrical seizures without return to baseline in between,</td>
<td></td>
</tr>
<tr>
<td>or motor findings&lt;sup&gt;c&lt;/sup&gt;:</td>
<td></td>
</tr>
<tr>
<td>• deep focal motor weakness such as hemiparesis or paraparesis,</td>
<td></td>
</tr>
<tr>
<td>or raised ICP / cerebral edema, with signs/symptoms such as:</td>
<td></td>
</tr>
<tr>
<td>• diffuse cerebral edema on neuroimaging, or</td>
<td></td>
</tr>
<tr>
<td>• decerebrate or decorticate posturing, or</td>
<td></td>
</tr>
<tr>
<td>• cranial nerve VI palsy, or</td>
<td></td>
</tr>
<tr>
<td>• papilledema, or</td>
<td></td>
</tr>
<tr>
<td>• Cushing’s triad</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.

<sup>a</sup> Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity.

<sup>b</sup> 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.

<sup>c</sup> All references to dexamethasone administration are dexamethasone or equivalent.

<sup>d</sup> 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.

<sup>e</sup> 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.
Peripheral Neuropathy

Patients may also experience peripheral neuropathy following CARVYKTI infusion

- Six patients from CARTITUDE-1 reported neuropathies of which the most common were peripheral sensory neuropathy (see Slide 29)
- Median time of onset of symptoms was 62 days (range 4 to 136 days), median duration of peripheral neuropathies was 256 days (range 2 to 465 days) including those with ongoing neuropathy
## Peripheral Neuropathy

<table>
<thead>
<tr>
<th>Study Number and Patient</th>
<th>Adverse Event Observed/Grade</th>
<th>Intervention Used</th>
<th>Outcome of Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTITUDE-1: Patient 1</td>
<td>Peripheral sensory neuropathy/2</td>
<td>None reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 2</td>
<td>Peripheral sensory neuropathy/2</td>
<td>None reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 3</td>
<td>Peripheral sensory neuropathy/1</td>
<td>None reported</td>
<td>Not applicable</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 4</td>
<td>Peripheral sensory neuropathy/2</td>
<td>None reported</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
| CARTITUDE-1: Patient 5   | Peripheral motor neuropathy/3  
Peroneal nerve palsy/3  
Peripheral motor neuropathy/2  
Peroneal nerve palsy/2       | dexamethasone  
dexamethasone         | Not improved  
Not improved  
Not applicable  
Not applicable         |
| CARTITUDE-1: Patient 6   | Peripheral sensory neuropathy/3  
Peroneal motor neuropathy/3  
Peripheral sensory neuropathy/2  
Peripheral motor neuropathy/2 | None reported      | Not applicable           |

29
Guillain-Barré Syndrome (GBS)

A fatal outcome following GBS has occurred in another ongoing study following infusion of ciltacabtagene autoleucel despite treatment with intravenous immunoglobulins

- Patients presenting with peripheral neuropathy following CARVYKTI infusion should be monitored for GBS and to consider treatment with supportive care in conjunction with immunoglobulins and plasma exchange depending on severity of GBS
Cranial Nerve Palsies

Patients may experience cranial nerve palsies following CARVYKTI infusion

- Three patients from CARTITUDE-1 reported cranial nerve palsies of which the most common were facial nerve palsies (see Slide 32)
- Median time to onset was 26 days (range 21 to 101 days). Median time to resolution was 70 days (range 1 to 79 days) following onset of symptoms
- Occurrence of 3rd and 6th cranial nerve palsy, bilateral 7th cranial nerve palsy, worsening of cranial nerve palsy after improvement and occurrence of peripheral neuropathy in patients with cranial nerve palsy have also been reported in ongoing trials ciltacabtagene autoleucel
## Cranial Nerve Palsies

<table>
<thead>
<tr>
<th>Study Number and Patient</th>
<th>Adverse Event Observed/Grade</th>
<th>Intervention Used</th>
<th>Outcome of Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARTITUDE-1: Patient 1</td>
<td>Facial paralysis/2</td>
<td>dexamethasone</td>
<td>Recovered</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 2</td>
<td>Facial paralysis/2</td>
<td>dexamethasone, hypromellose, methylprednisolone, prednisone, valacyclovir HCL</td>
<td>Recovered</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 3</td>
<td>Cranial nerve paralysis/3</td>
<td>dexamethasone, prednisone</td>
<td>Improved</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 3</td>
<td>Cranial nerve paralysis/3</td>
<td></td>
<td>Improved</td>
</tr>
<tr>
<td>CARTITUDE-1: Patient 3</td>
<td>Cranial nerve paralysis/2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Prolonged Cytopenias

- Patients may exhibit prolonged and recurrent cytopenias following lymphodepleting chemotherapy and CARVYKTI infusion
- In CARTITUDE-1 (N=97) Grade 3 or 4 cytopenias not resolved by Day 30:
  - Neutropenia 31% (29/97)
    - Of patients who recovered after 1 month (31%) median time to recovery was 1.8 months (range 1.0–3.7 months)
  - Thrombocytopenia 41% (40/97)
    - Of patients who recovered after one month (52%) median time to recovery was 1.9 months (range 1.1–8.5 months)
- One patient underwent *ASCT therapy for hematopoietic reconstitution due to prolonged thrombocytopenia

*ASCT – Autologous Stem Cell Transplant
Recurrent Cytopenias

- Recurrent Grade 3 or 4 cytopenia after recovery from initial Grade 3 or 4 cytopenia at any time:
  - Neutropenia - 63%
  - Thrombocytopenia - 18%
  - Lymphopenia - 60%
  - Anemia - 37%

- Recurrent Grade 3 or 4 cytopenia after recovery from initial Grade 3 or 4 cytopenia after Day 60:
  - Neutropenia - 12%
  - Thrombocytopenia - 6%
  - Lymphopenia - 31%

- Patients with 1, 2, 3, or more recurrences of Grade 3 or 4 cytopenias after initial recovery of Grade 3 or 4 cytopenia was 87% (84/97)

- Patients with Grade 3 or 4 cytopenia at time of death:
  - Neutropenia – n=6
  - Thrombocytopenia – n=11

- Monitor blood counts prior to and after CARVYKTI infusion. Manage cytopenias with growth factors and blood product transfusion support according to local institutional guidelines
Patient and Caregiver Education

- Advise patients and their caregivers of the risks of CRS and neurological toxicities and to contact their healthcare professional if experiencing signs or symptoms associated with CRS and neurological toxicities.
- Patients should be monitored daily for 10 days following the infusion at a certified Hospital and/or Associated Clinic and then periodically for 4 weeks.
- It is recommended that patients remain close to the location where treatment was received for at least 4 weeks following infusion.
- Before discharge, the patient or caregiver should be provided with the Patient Wallet Card through the processes and procedures established as a requirement of the REMS program.
- Patients should carry the Patient Wallet Card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate medical attention.
- Patients receiving CARVYKTI are at risk for altered or decreased consciousness or coordination in the 8 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 neurological symptoms.
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

• Healthcare providers must report any serious adverse event* including those suggestive of CRS or neurological toxicities to Janssen, Biotech Inc at 1-800-Janssen (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
Additional CARVYKTI REMS Information

For further information, please visit www.CARVYKTI.REMS.com or call 1-844-672-0067
Management of Cytokine Release Syndrome (CRS)
If CRS is suspected, manage according to the recommendations in Table 1. Administer supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) as appropriate. Consider intensive care unit level monitoring and supportive therapy, for severe or life-threatening CRS. Consider laboratory testing to monitor for disseminated intravascular coagulation, hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function. Other monoclonal antibodies targeting cytokines (for example, anti-IL1 and/or anti-TNFα) or therapy directed at reduction and elimination of CAR-T cells may be considered for patients who develop high grade CRS and hemophagocytic lymphohistiocytosis (HLH) that remains severe or life-threatening following prior administration of tocilizumab and corticosteroids. 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-TNFα, 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
• Antiseizure medication according to the neurologic toxicity in Table 2
### Table 1: Cytokine Release Syndrome Management Algorithm

<table>
<thead>
<tr>
<th>CRS Grade</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong>&lt;br&gt;Temperature ≥38°C (100.4°F)&lt;br&gt;• 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</td>
<td>In patients with:</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Grade 2</strong>&lt;br&gt;Symptoms require and respond to moderate intervention.&lt;br&gt;Temperature ≥38°C (100.4°F) with:&lt;br&gt;• Hypotension not requiring vasopressors, and/or,&lt;br&gt;• Hypoxia requiring oxygen via canula or blow-by, or,&lt;br&gt;• Grade 2 organ toxicity</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><strong>Grade 3</strong>&lt;br&gt;Symptoms require and respond to aggressive intervention.&lt;br&gt;Temperature ≥38°C (100.4°F) with:&lt;br&gt;• Hypotension requiring one vasopressor with or without vasopressin, and/or,&lt;br&gt;• Hypoxia requiring oxygen via high-flow nasal canula, facemask, non-rebreather mask, or Venturi mask, or,&lt;br&gt;• Grade 2 organ toxicity</td>
<td>Per Grade 2</td>
<td>Administer dexamethasone 10 mg IV every 12 hours.</td>
</tr>
<tr>
<td><strong>Grade 4</strong>&lt;br&gt;Life-threatening symptoms.&lt;br&gt;Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD).&lt;br&gt;Temperature ≥38°C (100.4°F) with:&lt;br&gt;• Hypotension requiring multiple vasopressors (excluding vasopressin), and/or,&lt;br&gt;• Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation, and mechanical ventilation), or,&lt;br&gt;• Grade 4 organ toxicity (excluding transaminitis).</td>
<td>Per Grade 2</td>
<td>Administer dexamethasone 20 mg IV every 6 hours.</td>
</tr>
</tbody>
</table>

* Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity.

* Refer to tocilizumab prescribing information for details.

* 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.

* Monoclonal antibodies targeting cytokines may be considered based on institutional practice for unresponsive CRS.

* Low-flow nasal cannula is ≤6 L/min; high-flow nasal cannula is >6 L/min.

* Continue corticosteroids use until the event is Grade 1 or less; taper steroids if total corticosteroid exposure is greater than 3 days.

* Organ toxicity grading based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.
Neurologic Toxicities

General management for neurologic toxicity (e.g., Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)) and other neurotoxicities is summarized in Table 2. Rule out other causes of neurologic signs or symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities.

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

Table 2: Guidelines for the Management of ICANS

<table>
<thead>
<tr>
<th>ICANS Grade</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
</tr>
<tr>
<td>ICE score 7-9 &lt;sup&gt;a&lt;/sup&gt; or depressed level of consciousness: awakens spontaneously.</td>
<td>Consider dexamethasone&lt;sup&gt;c&lt;/sup&gt; 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>Grade 2</td>
<td></td>
</tr>
<tr>
<td>ICE score 3-6 &lt;sup&gt;b&lt;/sup&gt; or depressed level of consciousness: awakens to voice.</td>
<td>Administer dexamethasone&lt;sup&gt;c&lt;/sup&gt; 10 mg intravenously every 6 hours for 2-3 days, or longer for persistent symptoms. Consider steroid taper if total corticosteroid exposure is greater than 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 (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
</tr>
<tr>
<td>ICE score 0-2 &lt;sup&gt;c&lt;/sup&gt; (If ICE score is 0, but the patient is arousable (e.g. awake with global aphasia) and able to perform assessment) or depressed level of consciousness: awakens only to tactile stimulus, any clinical seizure, focal or generalized, that resolves rapidly, or non-convulsive seizures on EEG that resolve with intervention, or raised intracranial pressure (ICP): focal/local edema on neuroimaging&lt;sup&gt;d&lt;/sup&gt;.</td>
<td>Administer dexamethasone&lt;sup&gt;c&lt;/sup&gt; 10 mg-20 mg IV every 6 hours. If no improvement after 24 hours or worsening of neurologic toxicity, escalate dexamethasone&lt;sup&gt;c&lt;/sup&gt; 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. 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).</td>
</tr>
<tr>
<td>Grade 4</td>
<td></td>
</tr>
<tr>
<td>ICE score 0&lt;sup&gt;d&lt;/sup&gt; (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 (&gt;5 min), or repetitive clinical or electrical seizures without return to baseline in between, or motor findings&lt;sup&gt;e&lt;/sup&gt;: 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</td>
<td>Administer dexamethasone&lt;sup&gt;c&lt;/sup&gt; 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. 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.</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.

<sup>a</sup> Based on ASTCT 2019 grading system (Lee et al., 2019), modified to include organ toxicity.

<sup>b</sup> 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.

<sup>c</sup> All references to dexamethasone administration are dexamethasone or equivalent.

<sup>d</sup> 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.

<sup>e</sup> 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.

Please visit www.CARVYKTIREMS.com for further information and resources.
CARVYKTI™ RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Knowledge Assessment

Online: www.CARVYKTIREMS.com
By phone: 1-844-672-0067
By fax: 1-877-778-3865
E-mail: CARVYKTI@JanssenREMS.com

Hospital and Associated Clinics Information (All Fields Required)

Hospital and Associated Clinics Name: ________________________________
Hospital and Associated Clinics REMS ID: ________________________________
Address: ___________________________________________________________
City: ___________________ State: ___________________ Zip Code: ________________
Phone: (___) ___-____ Fax: (___) ___-____

First Name: ___________________ Last Name: ___________________
Credentials:  □ MD  □ DO  □ R.Ph/PharmD  □ NP/PA  □ Other (please specify) __________
Phone: (___) ___-____ Fax: (___) ___-____ e-mail: ___________________

Authorized Representative:  □ Yes  □ No

__________________________________________  ____________
Signature  Date (MM/DD/YYYY)

To Be Completed by the Authorized Representative

Please indicate what questions were answered correctly by writing yes (Y) or no (N) below.

<table>
<thead>
<tr>
<th>Knowledge Assessment Attempt</th>
<th>QUESTION</th>
<th>TOTAL GRADE (example: 7/13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>2  3  4  5  6  7  8  9  10 11 12 13</td>
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<tr>
<td>2</td>
<td></td>
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</tr>
<tr>
<td>3</td>
<td></td>
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</tr>
</tbody>
</table>

All REMS-trained staff have 3 attempts to complete this Knowledge Assessment. After the third attempt, s/he must repeat REMS Training before repeating the Knowledge Assessment.

As a condition of certification, the Hospital and Associated Clinics Authorized Representative (AR) must complete the Knowledge Assessment. Additionally, all relevant Hospital and Associated Clinic staff involved in prescribing, dispensing, or administering CARVYKTI should complete this Knowledge Assessment. All questions must be answered correctly. The Knowledge Assessment can be completed online at www.CARVYKTIREMS.com or a completed hard copy can be submitted via fax to 1-877-778-3865 or e-mail at CARVYKTI@JanssenREMS.com. Completion of this Knowledge Assessment does not guarantee your Hospital and Associated Clinics will be certified to administer CARVYKTI.
1. Choose the correct answer. CARVYKTI is indicated for the treatment of:
A- Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma.
B- Adult patients with relapsed or refractory multiple myeloma after 4 or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.
C- Adult patients with multiple sclerosis who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.
D- Pediatric and young adult patients up to 25 years of age with relapsed refractory non-Hodgkin lymphoma (NHL).

2. Cytokine release syndrome (CRS) is the most common adverse event observed with CARVYKTI. Risk factors for severe CRS include the following:
A- High pre-infusion tumor burden
B- Active infection
C- Persistent fever after 24-hours of symptomatic treatment
D- Early onset of fever
E- All of the above

3. Patients with CRS may present with the following signs and symptoms, except:
A- High grade fever
B- Hypotension
C- Skin ulcers
D- Respiratory distress
E- Tachycardia

4. Which one of the following is true regarding the time to onset of CRS for CARVYKTI? It typically occurs:
A- 1-12 days following infusion, with a median time to onset of 7 days
B- 7-21 days following infusion, with a median time to onset of 10 days
C- 1-5 days following infusion, with a median time to onset of 3 days
D- Rarely starts during the first week following CARVYKTI infusion

5. As a part of planning for infusion, it is required to have 2 doses of tocilizumab on site for each patient prior to dispensing and administering CARVYKTI to patients:
A- True
B- False

6. All of the following regarding Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) are correct except:
A- ICANS always occurs concurrently with CRS
B- Patients should be monitored for signs or symptoms of ICANS for at least 4 weeks after infusion and treated promptly
C- The median time to onset of ICANS was 8 days (range: 1 to 28 days) and the median duration was 7.5 days
D- The most common signs or symptoms of ICANS included aphasia, slow speech, dysgraphia, encephalopathy, depressed level of consciousness, and confusional state

7. As a part of patient/caregiver counseling, which of the following are correct regarding CARVYKTI:
A- Before discharge, the Patient Wallet Card must be provided through the processes and procedures established as a requirement of the REMS program
B- Patients should remain close to the location where treatment was received for at least 4-weeks following infusion
C- Patients should seek immediate medical attention if they experience signs and symptoms of CRS or neurological toxicities
D- All of the above

8. A 50-year-old male presents 90 days following CARVYKTI infusion with right hand tremor and occasional falls. His wife states that he appears withdrawn over the last 2-3 weeks. On physical exam, you notice flat affect, stooped posture and cog-wheel rigidity. Other features of this neurologic toxicity include:
A- Micrographia
B- Memory loss
C- Bradykinesia
D- All of the above

9. Five (5) days after infusion with CARVYKTI, a 68-year-old man with relapsed multiple myeloma experiences fever and hypotension that responds to IV (intravenous) fluids. The next day, he experiences hypotension requiring vasoressors. The same day he experiences obtundation, aphasia, impaired ability to read or write, and difficulty communicating. What is/are the appropriate next step(s) in management for this patient?
A- Start tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)
B- Start dexamethasone at 10 mg IV every 6 hours
C- Consider non-sedating, antiseizure medicines (e.g. levetiracetam) for seizure prophylaxis
D- All of the above

10. Seven (7) days after infusion of CARVYKTI, a 58-year-old woman with relapsed multiple myeloma develops fever (38ºC [100.4ºF]). The next day, she develops the following signs and symptoms: fever of 40ºC (104ºF), hypotension, fatigue, headache. The patient was treated with tocilizumab 8 mg/kg IV over 1-hour and IV fluids, and symptoms improved the following day. This patient’s diagnosis and grade would be most consistent with:
A- Grade 1 Hypotension
B- Grade 2 CRS
C- Grade 3 CRS
D- Grade 1 ICANS
A 64-year-old male developed fever of 39°C (102.2°F) and 10 mmHg drop in his systolic BP from baseline 2 days after receiving CARVYKTI. He is deemed to have Grade 2 CRS and a single dose of tocilizumab 8 mg/kg and IV fluids are administered. On day 3, he continues to have high grade fever, worsening hypotension requiring a single vasopressor agent, hypoxia requiring oxygen 2 L/min via nasal canula and cytopenias. The next step in management of this patient:

A- Evaluate for Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
B- Optimize management of CRS with additional doses of anti-IL6 agent and addition of corticosteroids
C- Optimize anti-infective therapy
D- All of the above

A 55-year-old male with Grade 1 pre-existing peripheral sensory neuropathy following VRd (bortezomib, lenalidomide, dexamethasone) therapy for multiple myeloma presents to the emergency room (ER) 17 days following CARVYKTI infusion with complaints of drooping of angle of mouth bilaterally. He is diagnosed with bilateral facial nerve palsy and is treated with high dose glucocorticoids for 3 days with improvement of symptoms. Steroids are subsequently tapered and bilateral facial nerve palsy resolves. 3 months later, he presents to the ER with upper respiratory tract infection, worsening sensory loss in both lower extremities, weakness in both lower extremities and some difficulty swallowing. He is admitted and re-started on glucocorticoids and given IV Ig (intravenous immunoglobulin) for a presumed diagnosis of Guillain-Barre syndrome (GBS). Laboratory work-up to assess status of his myeloma shows negative SPEP, UPEP and IFE (Serum and urine protein electrophoresis and serum immunofixation). The patient asks you about his neurologic symptoms following CARVYKTI infusion. Which one of the following statements is correct:

A- Patient had idiopathic facial nerve palsy and there is no relation of occurrence of either facial nerve palsy or GBS to CARVYKTI infusion
B- Cranial nerve palsy, especially of the VII cranial nerve, and GBS have been reported following CARVYKTI infusion
C- Facial nerve palsy is not related to CARVYKTI infusion and worsening of sensory neuropathy and new onset motor neuropathy are related to prior chemotherapy for myeloma
D- Neurologic symptoms are related to progressive multiple myeloma
CARVKYT™ Risk Evaluation and Mitigation Strategy (REMS)

What is the CARVKYT REMS?
A Risk Evaluation and Mitigation Strategy (REMS) is a program to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration (FDA).

The FDA has determined that a REMS is necessary to ensure that the benefits of CARVKYT outweigh the risks of cytokine release syndrome and neurological toxicities. The FDA has required a REMS for CARVKYT.

BOXED WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES, HLH/MAS and PROLONGED and RECURRENT CYTOPENIA
Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients following treatment with CARVKYT. Do not administer CARVKYT 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 CARVKYT, including before CRS onset, concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with CARVKYT. Provide supportive care and/or corticosteroids as needed.

Panhypopituitarism syndrome and their associated complications resulting in fatal or life-threatening reactions have occurred following treatment with CARVKYT.

Neutrophilic Lymphohistiocytosis/Macrophage Activation Syndrome (HLH/MAS), including fatal and life-threatening reactions, occurred in patients following treatment with CARVKYT. 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 CARVKYT.

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

Goals of the REMS
The goal of the CARVKYT REMS is to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

- Ensuring that hospitals and their Associated Clinics that dispense CARVKYT are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring those who prescribe, dispense, or administer CARVKYT are aware of how to manage the risks of CRS and neurological toxicities.

Hospitals and their Associated Clinics
Hospitals and their Associated Clinics must be certified in the CARVKYT REMS in order to treat patients with CARVKYT.

Hospital and Associated Clinics Certification

Indication
CARVKYT is a B-Cell maturation antigen (BCMA)-directed genetically modified autologous T-cell immunotherapy indicated for the treatment of adult patients with either refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD19 monoclonal antibody.

Access CARVKYT REMS Materials and Enrollment in the CARVKYT REMS

Authorized Representatives

Access Training Program and Knowledge Assessment

Hospital and their Associated Clinics Staff

Resources for Healthcare Professionals
- Inclusion Enrollment Form
- GI Adverse Reaction Management Guide
- Knowledge Assessment
- Patient Wallet Card

Download All Resources

Resources for Patients
All patients treated with CARVKYT receive a Patient Wallet Card. Patients should carry the Wallet Card to remind them of the signs and symptoms of CRS and neurological toxicities that require immediate medical attention. Patients can share this card with any healthcare provider who provides care to them to inform them of receipt of CARVKYT treatment and when to contact the patient’s oncologist.

- Patient Wallet Card

Reporting Adverse Reactions
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 neurological toxicities contact Janssen Biotech, Inc at 1-800-JANSSEN (1-800-527-7736) or FDA at 1-888-INFO-FDA (1-888-466-3322) or www.fda.gov/reportad

Healthcare providers are also encouraged to report any suspected serious adverse events associated with CARVKYT 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/defect

Have Questions?
Contact the CARVKYT REMS by calling 1-844-672-0667
Hospitals and their Associated Clinics

CARVKTI REMS Requirements

Hospitals and their Associated Clinics must be certified in the CARVKTI REMS and have on-site, immediate access to tocilizumab to be able to dispense CARVKTI.

All relevant Hospitals and their Associated Clinics staff involved in the prescribing, dispensing, or administering of CARVKTI are trained on the CARVKTI REMS requirements, and must successfully complete the Knowledge Assessment. The designated Authorized Representative will determine relevant staff who require training.

How does my Hospital and Associated Clinics become certified in the CARVKTI REMS?

1. Step 1: Designate an Authorized Representative to complete the certification process and oversee implementation and compliance with the CARVKTI REMS on behalf of the Hospital and Associated Clinics

2. Step 2: Have the Authorized Representative review the following materials:
   - Training Program
   - Adverse Reaction Management Guide

3. Step 3: Have the Authorized Representative successfully complete the Knowledge Assessment and submit it to the REMS program
   - Online  |  By e-mail or Fax

4. Step 4: Have the Authorized Representative complete the Hospital Enrollment Form and submit it to the REMS program
   - Online  |  By e-mail or Fax

5. Step 5: Oversee implementation and compliance with the CARVKTI REMS:
   a. Ensure all relevant staff involved in the prescribing, dispensing, or administering of CARVKTI are trained on the REMS program requirements using the Training Program and the Adverse Reaction Management Guide and successfully complete the Knowledge Assessment
   b. Have on-site, immediate access to at least two doses of tocilizumab for each patient, for administration within 2 hours after infusion
   c. Have all relevant staff involved in prescribing, dispensing, or administering CARVKTI successfully complete the Knowledge Assessment
   d. Establish processes and procedures to ensure new staff involved in the prescribing, dispensing, or administration of CARVKTI are trained and complete the Knowledge Assessment
   e. Establish processes and procedures to provide patients with the Patient Wallet Card
   f. Prior to dispensing CARVKTI, put processes and procedures in place to verify on-site, immediate access to at least two doses of tocilizumab for each patient for administration within two hours after infusion
   g. Before discharge, provide patients or their caregivers with the Patient Wallet Card and processes and procedures established as a requirement of the REMS program and instruct them to remain close to the location where treatment was received for at least 4 weeks following infusion
   h. Perform re-education of all staff involved in the prescribing, dispensing, or administering of CARVKTI on the REMS requirements using the Training Program, the Adverse Reaction Management Guide; and having staff successfully complete the Knowledge Assessment, if CARVKTI has not been infused at least once annually from the date of certification of the Hospital and Associated Clinics in the CARVKTI REMS
   i. Establish processes and procedures that are subject to monitoring by Janssen Biotech, Inc. or a third-party acting on behalf of Janssen Biotech, Inc. to ensure compliance with the requirements of the REMS program

If the Hospital and Associated Clinics designates a new Authorized Representative, the new Authorized Representative must review the Training Program, the Adverse Reaction Management Guide, complete the Knowledge Assessment, and complete a new Hospital Enrollment Form.
Login / Register

Don't have an online account?

Register
To create your web account for the CARVYKTI REMS, please begin by completing the field(s) below and click "Continue".

*I am a(n)
- Authorized Representative
- Hospital and Associated Clinics Staff

*Hospital and Associated Clinics REMS ID

If you have questions about the CARVYKTI REMS or need help enrolling,
call 1-844-672-0067
Monday – Friday, 8:00 AM – 8:00 PM ET

Return to CARVYKTI REMS Homepage

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Don't have an online account?

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* I am a(n)
  - Authorized Representative
  - Hospital and Associated Clinics Staff

* Hospital and Associated Clinics REMS ID

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