YESCARTA and TECARTUS REMS Program Knowledge Assessment

To become an authorized representative for your hospital and its associated clinics in the YESCARTA and TECARTUS REMS Program, you will need to answer all questions below correctly.

All other REMS trained staff must also answer all questions correctly.

Responses to the YESCARTA and TECARTUS REMS Program Knowledge Assessment questions and the YESCARTA and TECARTUS REMS Hospital Enrollment Form must be emailed to YTREMS@kitepharma.com or faxed to 1-310-496-0397 or completed online at www.KiteREMSTraining.com.

Questions

1. Prior to discharge, a YESCARTA and TECARTUS REMS Patient Wallet Card must be given to patients or the caregiver of those patients who have been infused with YESCARTA or TECARTUS.
   True ______ False ______

2. Every certified hospital and its associated clinics are required to have immediate access to a minimum of 2 doses of tocilizumab on-site for each patient and available for administration, for treatment of cytokine release syndrome (CRS), within 2 hours of YESCARTA or TECARTUS infusion.
   True ______ False ______

3. After YESCARTA or TECARTUS infusion, patients should be advised to:
   A. Refrain from driving or operating heavy or potentially dangerous machinery for at least 8 weeks after YESCARTA or TECARTUS infusion
   B. Remain within close proximity (within 2 hours) of the certified treating hospital and its associated clinics for at least 4 weeks following infusion
   C. Seek immediate attention if they experience signs and symptoms of CRS and/or neurological toxicities
   D. All of the above

4. Which of the following is true regarding the time to onset of CRS? (select one)
   A. Median time to onset of CRS following YESCARTA infusion is 2-5 days
   B. Median time to onset of CRS following TECARTUS infusion is 3-5 days
   C. CRS rarely starts during the first week following YESCARTA or TECARTUS infusion
   D. A & B

5. Which of the following is true regarding the time to onset of neurotoxicity? (select one)
   A. Median time to onset of neurotoxicity following YESCARTA infusion is 4-6 days
   B. Neurotoxicity rarely starts during the first week following YESCARTA or TECARTUS infusion
   C. Median time to onset of neurotoxicity following TECARTUS infusion is 6-7 days
   D. A & C

Continued on Back
6. All of the following regarding neurologic toxicity related to YESCARTA or TECARTUS are correct except:
   A. Neurologic toxicity always occurs concurrently with CRS
   B. Continuous cardiac telemetry and pulse oximetry are recommended for Grade 2 or higher neurologic toxicity
   C. The median time to onset of neurologic toxicity is 4-6 days for patients with LBCL and 6 days for patients with iNHL following YESCARTA infusion
   D. The median time to onset of neurologic toxicity is 6 days for patients with MCL and 7 days for patients with ALL following TECARTUS infusion

7. Four days after infusion with YESCARTA, a 49-year-old woman with relapsed diffuse large B-cell lymphoma (DLBCL) fully recovers from a Grade 3 CRS that started the day after infusion of YESCARTA. The next day, she develops a Grade 2 dysphasia. She has no signs or symptoms of CRS. Per the REMS Program Training, appropriate management for this patient would include (please select single best answer):
   A. Consider levetiracetam for seizure prophylaxis
   B. Start tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg)
   C. Start dexamethasone 10 mg intravenously four times a day
   D. A and C

8. One day after infusion of TECARTUS, a 60-year-old man with mantle cell lymphoma (MCL) develops the following signs and symptoms of CRS: high fever (39-40°C), hypoxia requiring <40% FiO₂, and hypotension requiring intravenous fluids. According to the modified Lee Grading Scale as defined in the REMS Program Training, this patient’s CRS grade would be most consistent with:
   A. Grade 1 CRS
   B. Grade 2 CRS
   C. Grade 3 CRS
   D. Grade 4 CRS
Please Complete All Fields Below

Name

Title

Credentials DO _____ MD _____ RPh _____ RN_____ NP/PA _____ Other ___________

Hospital/Associated Clinic Name

Address

City

State

ZIP Code

Signature

Date
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<tr>
<td>1</td>
<td><strong>YESCARTA® and TECARTUS® Risk Evaluation and Mitigation Strategy (REMS) Program Training</strong></td>
<td>N/A</td>
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<td>2</td>
<td>The educational module contains information on adverse reactions associated with YESCARTA and TECARTUS, including cytokine release syndrome and neurologic toxicities. These are not all of the adverse reactions associated with YESCARTA and TECARTUS.</td>
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| 3                     | **Indication - YESCARTA®**  
YESCARTA® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:  
Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.  
Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.  
Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.  
Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate.  
Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).  
Please see full Prescribing Information, including BOXED WARNING and Medication Guide. | N/A                |                        |
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<td>4</td>
<td><strong>Indication – TECARTUS®</strong>&lt;br&gt;TECARTUS® is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:&lt;br&gt;Adult patients with relapsed or refractory mantle cell lymphoma (MCL). This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.&lt;br&gt;Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).&lt;br&gt;<strong>Please see full Prescribing Information, including BOXED WARNING and Medication Guide.</strong></td>
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<td>5</td>
<td><strong>YESCARTA and TECARTUS REMS Program Overview</strong></td>
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<td>6</td>
<td><strong>What is the YESCARTA and TECARTUS REMS (Risk Evaluation and Mitigation Strategy) Program?</strong>&lt;br&gt;A REMS Program is a strategy to manage known or potential risks associated with a drug and is required by the United States (US) Food and Drug Administration (FDA) to ensure that the benefits of the drug outweigh its risks. YESCARTA and TECARTUS are available only under a program called the YESCARTA and TECARTUS REMS Program because of the serious risks of cytokine release syndrome (CRS) and neurologic toxicities.&lt;br&gt;The goals of the YESCARTA and TECARTUS REMS Program are to mitigate the risks of CRS and neurologic toxicities by:&lt;br&gt;• Ensuring that hospitals and their associated clinics that dispense YESCARTA and/or TECARTUS are specially certified and have on-site, immediate access to a minimum of 2 doses of tocilizumab&lt;br&gt;• Ensuring that those relevant individuals who prescribe, dispense, or administer YESCARTA and/or TECARTUS are</td>
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<td><strong>Hospital Certification</strong>&lt;br&gt;To become certified to dispense YESCARTA and/or TECARTUS, hospitals and their associated clinics must:&lt;br&gt;1) Designate an authorized representative to complete the training program by completing and submitting the YESCARTA and TECARTUS REMS Program Hospital Enrollment Form on behalf of the hospital and its associated clinics&lt;br&gt;2) Ensure that the authorized representative oversees implementation and compliance with the YESCARTA and TECARTUS REMS Program requirements&lt;br&gt;3) Dispense YESCARTA and/or TECARTUS only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for administration within 2 hours&lt;br&gt;4) Recertify in the YESCARTA and TECARTUS REMS Program if a new authorized representative is designated.</td>
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<td>8</td>
<td><strong>Hospital Certification (continued)</strong>&lt;br&gt;5) Maintain documentation that all processes and procedures are in place and are being followed for the YESCARTA and TECARTUS REMS Program; provide this documentation upon request to Kite, or a third party acting on behalf of Kite or FDA&lt;br&gt;6) Comply with audits by Kite, or a third party acting on behalf of Kite or FDA, to ensure that all training, processes, and procedures are in place and are being followed for the YESCARTA and TECARTUS REMS Program&lt;br&gt;7) Report any serious adverse events* suggestive of CRS or neurologic toxicities&lt;br&gt;* 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 event, hospitalization or prolongation of existing hospitalization, life-threatening organ/system dysfunction or damage, persistent or significant disability/incapacity, significant economic loss, or a congenital anomaly/birth defect, or a serious adverse event that is considered to be related to study therapy.</td>
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| 9                      | **Who Can Be an Authorized Representative?**  
                          An authorized representative at the hospital and its associated clinics can be a:  
                          • Physician  
                          • Nurse  
                          • Any responsible individual assigned by the hospital and its associated clinics  
                          One representative (the “authorized representative”) must enroll for each hospital and its associated clinics and attest to the enrollment requirements as stated on the YESCARTA and TECARTUS REMS Program Hospital Enrollment Form. |                     | N/A                    |
| 10                     | **YESCARTA and TECARTUS REMS Authorized Representative Attestations**  
                          • Complete the YESCARTA and TECARTUS REMS Program Training and successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment  
                          • Submit the completed YESCARTA and TECARTUS REMS Program Hospital Enrollment Form to Kite via fax at 1-310-496-0397, email to YTREMS@kitepharma.com, or online at www.KiteREMSTraining.com  
                          • Submit the YESCARTA and TECARTUS REMS Program Knowledge Assessment online on the REMS Program Training website or send to Kite via fax at 1-310-496-0397 or email to YTREMS@kitepharma.com  
                          Oversee implementation and compliance with the YESCARTA and TECARTUS REMS Program                                                      |                     | N/A                    |
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<td>11</td>
<td><strong>YESCARTA and TECARTUS REMS Authorized Representative Attestations (continued)</strong></td>
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<td>• Ensure that the hospital and its associated clinics will establish processes and procedures that are subject to monitoring by Kite or a third party acting on behalf of Kite to help ensure compliance with the requirements of the YESCARTA and TECARTUS REMS Program, including the following, before administering YESCARTA and/or TECARTUS:</td>
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<td>- Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA and/or TECARTUS are trained on the REMS Program requirements as described in the training materials, successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment, and maintain training records for all staff. The Authorized Representative will determine relevant staff who require training</td>
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<td>- Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing, or administering of YESCARTA and/or TECARTUS are retrained if YESCARTA or TECARTUS has not been dispensed at least once annually from the date of certification in the YESCARTA and TECARTUS REMS Program</td>
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<td>- Prior to dispensing YESCARTA and/or TECARTUS, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours)</td>
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<td>- Prior to patient discharge, provide patients/caregivers with the Patient Wallet Card</td>
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<td><strong>Serious Risks of YESCARTA and TECARTUS</strong></td>
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| 13                    | Serious Risks Associated With YESCARTA  
BOXED WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES  
- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids  
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids as needed | N/A | N/A |
| 14                    | Serious Risks Associated With TECARTUS  
BOXED WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES  
- Cytokine Release Syndrome (CRS), including life-threatening reactions, occurred in patients receiving TECARTUS. Do not administer TECARTUS to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids  
- Neurologic toxicities, including life-threatening reactions, occurred in patients receiving TECARTUS, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with TECARTUS. Provide supportive care and/or corticosteroids, as needed | N/A | N/A |
<p>| 15                    | Management of CRS | N/A | N/A |</p>
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<th>Cytokine Release Syndrome - YESCARTA</th>
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<td>• CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA</td>
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<td>• CRS occurred in 90% (379/422) of patients with non-Hodgkin lymphoma (NHL) receiving YESCARTA, including ≥ Grade 3 CRS in 9%</td>
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<td>• CRS occurred in 93% (256/276) of patients with large B-cell lymphoma (LBCL), including ≥ Grade 3 CRS in 9%</td>
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<td>• CRS occurred in 84% (123/146) of patients with indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5, including ≥ Grade 3 CRS in 8%</td>
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<td>• For patients with LBCL, the median time to onset of CRS in:</td>
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<td>o ZUMA-1 was 2 days following infusion (range: 1-12 days)</td>
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<td>o ZUMA-7 was 3 days following infusion (range: 1-10 days)</td>
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<td>For patients with iNHL, the median time to onset of CRS was 4 days (range: 1-20 days)</td>
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<td>• For patients with LBCL, the median duration of CRS in:</td>
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<td>o ZUMA-1 was 7 days (range: 2-58 days)</td>
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<td>o ZUMA-7 was 7 days (range: 2-43 days)</td>
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<td>For patients with iNHL, the median duration of CRS was 6 days (range: 1-27 days)</td>
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<td>• 45% (49/108) of patients with LBCL in ZUMA-1, and 67% (112/168) of patients with LBCL in ZUMA-7 received tocilizumab after infusion of YESCARTA</td>
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<td>• 51% (75/146) of patients with iNHL received tocilizumab after infusion of YESCARTA</td>
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<td>• Among patients who died after receiving YESCARTA, 4 LBCL patients and 1 iNHL patient had ongoing CRS events at the time of death</td>
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<td>o Serious events that may be associated with CRS include, cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), renal insufficiency, cardiac failure, respiratory failure, cardiac</td>
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<td>arrest, capillary leak syndrome, multi-organ failure and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)</td>
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| N/A                   | Cytokine Release Syndrome – YESCARTA (continued)  
  • The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of CRS was assessed in two subsequent cohorts of LBCL patients (ZUMA-1).  
  Among patients who received tocilizumab and/or corticosteroids for ongoing Grade 1 events:  
  o CRS occurred in 93% (38/41) including 2% (1/41) with Grade 3 CRS; no patients experienced a Grade 4 or 5 event  
  o The time to onset of CRS was 2 days (range: 1-8 days)  
  o The median duration of CRS was 7 days (range: 2-16 days)  
  Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA:  
  o Thirty-one out of the 39 patients (79%) developed CRS with no patients developing Grade 3 or higher CRS  
  o The median time to onset of CRS was 5 days (range: 1-15 days)  
  o The median duration of CRS was 4 days (range: 1-10 days)  
  o Although there is no known mechanistic explanation, consider the risk and benefits of prophylactic corticosteroids in the context of pre-existing comorbidities for the individual patient and the potential for the risk of Grade 4 and prolonged neurologic toxicities |                        | N/A                   |
### Slide 18: Cytokine Release Syndrome – TECARTUS

- CRS, including fatal or life-threatening reactions, occurred following treatment with TECARTUS
- CRS occurred in 91% (75/82) of patients with MCL, including ≥ Grade 3 (Lee grading system\(^1\)) CRS in 18% of patients
- CRS occurred in 92% (72/78) of patients with ALL, including ≥ Grade 3 (Lee grading system\(^1\)) CRS in 26% of patients
- Among the patients with MCL who died after receiving TECARTUS, 1 had a fatal CRS event. Three patients with ALL had ongoing CRS events at the time of death
- The median time to onset of CRS was 3 days (range, 1-13 days) for patients with MCL
- The median duration of CRS was 10 days (range, 1-50 days) for patients with MCL
- The median time to onset of CRS was 5 days (range, 1-12 days) for patients with ALL
- The median duration of CRS was 8 days (range, 2-63 days) for patients with ALL
- Serious events associated with CRS in MCL and ALL combined (≥ 2%) included hypotension, fever, hypoxia, tachycardia, and dyspnea


### Slide 19: Patient Assessment of CRS Associated with YESCARTA\(^1\)

The following are signs and symptoms of CRS in all patients combined

Chills
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<tr>
<td>1</td>
<td>Fatigue</td>
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<td>Fever</td>
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<td>Hypoxia</td>
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<td>Tachycardia</td>
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<td>¹Reference Section 5.1 (Warning and Precautions/CRS) of the YESCARTA Prescribing Information for a complete list of signs and symptoms for CRS</td>
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<td>20</td>
<td><strong>Patient Assessment of CRS Associated with TECARTUS¹</strong></td>
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<td>The key signs and symptoms of CRS associated with TECARTUS are similar in MCL and ALL and include:</td>
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<td>Nausea</td>
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<td>¹Reference Section 5.1 (Warning and Precautions/CRS) of the TECARTUS Prescribing Information for a complete list of signs and symptoms for CRS</td>
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<td>21</td>
<td><strong>Guidance on Managing CRS for YESCARTA</strong></td>
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<td></td>
<td>• Identify CRS based on clinical presentation</td>
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| • Evaluate for and treat other causes of fever, hypoxia, and hypotension  
• If CRS is suspected, manage according to the recommendations on slide 21  
• Tocilizumab, an interleukin-6 receptor antagonist, is recommended for the management of Grade 2 or higher CRS associated with YESCARTA  
• Patients who experience Grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry  
• For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function  
• For severe or life-threatening CRS, consider intensive care supportive therapy  
• Monitor patients at least daily for 7 days at the certified hospitals and their associated clinics following infusion for signs and symptoms of CRS  
• Monitor patients for signs or symptoms of CRS for 4 weeks after infusion                                                                 |                    | N/A                   |
| Guidance on Management of CRS for YESCARTA  
Grading and Management of YESCARTA-Related CRS  
[Guidance and Management Table per the YESCARTA and TECARTUS Adverse Reaction Management Guide]                                                                 |                    | N/A                   |
| Guidance on Managing CRS for TECARTUS  
• Identify CRS based on clinical presentation  
• Evaluate for and treat other causes of fever, hypoxia, and hypotension  
• If CRS is suspected, manage according to the recommendations on slide 23                                                                 |                    | N/A                   |
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<td>• Tocilizumab, an interleukin-6 receptor antagonist, is recommended for the management of Grade 1 or higher CRS associated with TECARTUS</td>
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<td>• Patients who experience Grade 2 or higher CRS (eg, hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry</td>
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<td>• For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function</td>
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<td>• For severe or life-threatening CRS, consider intensive care supportive therapy</td>
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<td>• Monitor patients daily for at least 7 days for patients with MCL and at least 14 days for patients with ALL at the certified hospitals and their associated clinics following infusion for signs and symptoms of CRS</td>
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<td>• Monitor patients for signs or symptoms of CRS for 4 weeks after infusion</td>
<td>24</td>
<td>Guidance on Management of CRS for TECARTUS</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grading and Management of TECARTUS-Related CRS</td>
<td>[Guidance and Management Table per the YESCARTA and TECARTUS Adverse Reaction Management Guide]</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Management of Neurologic Toxicities</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>Neurologic Toxicities - YESCARTA</td>
<td>Neurologic Toxicities - YESCARTA</td>
</tr>
<tr>
<td></td>
<td>• Neurologic toxicities/immune effector cell-associated neurotoxicity syndrome (ICANS) that were fatal or life-threatening occurred following treatment with YESCARTA</td>
<td>• Neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome (ICANS)) that were fatal or life-threatening occurred following treatment with YESCARTA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neurologic toxicities occurred in 78% (330/422) of patients with NHL receiving YESCARTA, including ≥ Grade 3 cases in 25%</td>
<td>• Neurologic toxicities occurred in 78% (330/422) of patients with NHL receiving YESCARTA, including ≥ Grade 3 cases in 25%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Neurologic toxicities occurred in 87% (94/108) of patients with LBCL in ZUMA-1, including ≥ Grade 3 cases in 31%</td>
<td>• Neurologic toxicities occurred in 87% (94/108) of patients with LBCL in ZUMA-1, including ≥ Grade 3 cases in 31%</td>
<td></td>
</tr>
</tbody>
</table>
and in 74% (124/168) of patients in ZUMA-7 including ≥ Grade 3 cases in 25%
- Neurologic toxicities occurred in 77% (112/146) of patients with iNHL, including ≥ Grade 3 in 21%
- Neurologic toxicities occurred within the first 7 days of YESCARTA infusion for 87% of affected patients with LBCL and 74% of affected patients with iNHL
- For patients with LBCL, the median time to onset of neurologic toxicities in:
  - ZUMA-1 was 4 days (range: 1-43 days)
  - ZUMA-7 was 5 days (range: 1-133 days)
For patients with iNHL, the median time to onset of neurologic toxicities was 6 days (range: 1-79 days)
- For patients with LBCL, the median duration of neurologic toxicities in:
  - ZUMA-1 was 17 days
  - ZUMA-7 was 15 days
For patients with iNHL, the median duration was 16 days
- Prolonged encephalopathy lasting up to 173 days was noted
- Serious events including aphasia, leukoencephalopathy, dysarthria, lethargy, and seizures occurred in patients treated with YESCARTA
- Fatal and serious cases of cerebral edema and encephalopathy, including late-onset encephalopathy, have occurred in patients treated with YESCARTA

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<th>Slide Number (Current)</th>
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</thead>
<tbody>
<tr>
<td>27</td>
<td>Neurologic Toxicities – YESCARTA (continued)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>• The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of neurologic toxicities was assessed in two subsequent cohorts of LBCL patients (ZUMA-1)</td>
<td></td>
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</tr>
</tbody>
</table>
Among patients who received corticosteroids at the onset of Grade 1 toxicities
- Neurologic toxicities occurred in 78% (32/41) and 20% (8/41) had Grade 3 neurologic toxicities; no patients experienced a Grade 4 or 5 event
- The median time to onset of neurologic toxicities was 6 days (range, 1-93 days)
- The median duration was 8 days (range, 1-144 days)

Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA:
- Thirty-three out of the 39 patients (85%) developed neurologic toxicities and 8% (3/39) developed Grade 3 and 5% (2/39) developed Grade 4 neurologic toxicities
- The median time to onset of neurologic toxicities was 6 days (range, 1-274 days)
- The median duration of 12 days (range, 1-107 days)
- Prophylactic corticosteroids for management of CRS and neurologic toxicities may result in higher grade of neurologic toxicities or prolongation of neurologic toxicities, delay the onset and decrease the duration of CRS

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<tr>
<th>Slide Number (Current)</th>
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</thead>
</table>
| 28 | **Neurologic Toxicities - TECARTUS**  
- Neurologic events, including those that were fatal or life-threatening, occurred following treatment with TECARTUS  
- Neurologic events occurred in 81% (66/82) of patients with MCL including ≥ Grade 3 in 37% of patients  
- Neurologic events occurred in 87% (68/78) of patients with ALL, including ≥ Grade 3 in 35% of patients | N/A | N/A |
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<th>Proposed Content (new)</th>
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</table>
| • Ninety-one percent of all treated patients (MCL/ALL) experienced the first CRS or neurological event within the first 7 days after TECARTUS infusion  
• Nine patients (3 patients with MCL and 6 patients with ALL) had ongoing neurologic events at the time of death  
• The median time to onset was 6 days (range, 1-32 days) in patients with MCL  
• The median duration was 21 days (range, 2-454 days) in patients with MCL  
• The median time to onset was 7 days (range, 1-51 days) in patients with ALL  
• The median duration was 15 days (range, 1-397 days) in patients with ALL  
• Serious events (≥ 2%) including encephalopathy, aphasia, confusional state, and seizures occurred after treatment with TECARTUS | | | |
| 29 Patient Assessment of Neurologic Toxicities Associated With YESCARTA¹ | The following are common signs and symptoms of neurologic toxicities in all patients combined  
Aphasia  
Delirium  
Dizziness  
Encephalopathy  
Headache  
Insomnia  
Tremor | | N/A |
<table>
<thead>
<tr>
<th>Slide Number (Current)</th>
<th>Current Content</th>
<th>Slide Number (new)</th>
<th>Proposed Content (new)</th>
</tr>
</thead>
</table>
| 30                     | Patient Assessment of Neurologic Toxicities Associated With TECARTUS<sup>1</sup>  
The most common neurologic events associated with TECARTUS are similar in MCL and ALL and include:  
Agitation  
Anxiety  
Aphasia  
Confusional state  
Delirium  
Dizziness  
Encephalopathy  
Headache  
Tremor  
<sup>1</sup>Reference Section 5.2 (Warning and Precautions/Neurologic Toxicities) of the TECARTUS Prescribing Information for a complete list of signs and symptoms for neurologic toxicities | N/A                | N/A                    |

31 Guidance on Managing Neurologic Toxicities for YESCARTA and TECARTUS  
- Monitor patients for signs and symptoms of neurologic toxicities  
- Rule out other causes of neurologic symptoms  
- Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry | N/A                | N/A                    |
<table>
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<tr>
<th>Slide Number (Current)</th>
<th>Current Content</th>
<th>Slide Number (new)</th>
<th>Proposed Content (new)</th>
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<tbody>
<tr>
<td></td>
<td>• Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Consider levetiracetam for seizure prophylaxis for any grade of neurologic toxicities for patients treated with YESCARTA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Consider levetiracetam for seizure prophylaxis for any Grade 2 of neurologic toxicities for patients treated with TECARTUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Monitor patients at least daily for 7 days for patients treated with YESCARTA at the certified hospitals and their associated clinics following infusion for signs and symptoms of neurologic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Monitor patients at least daily for 7 days for patients treated with TECARTUS for MCL and at least 14 days for patients treated with TECARTUS for ALL at the certified hospitals and their associated clinics following infusion for signs and symptoms of neurologic toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td><strong>Guidance on Managing Neurologic Toxicities for YESCARTA</strong></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Grading and Management of YESCARTA-Related Neurologic Toxicities</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>[Grading and Management Table – per the YESCARTA and TECARTUS Adverse Reaction Management Guide for Grade 1 and Grade 2]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33</td>
<td><strong>Guidance on Managing Neurologic Toxicities for YESCARTA</strong> (continued)</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>[Grading and Management Table – per the YESCARTA and TECARTUS Adverse Reaction Management Guide for Grade 3 and Grade 4]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td><strong>Guidance on Managing Neurologic Toxicities for TECARTUS</strong></td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Slide Number (Current)</td>
<td>Current Content</td>
<td>Slide Number (new)</td>
<td>Proposed Content (new)</td>
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<td>------------------------</td>
</tr>
<tr>
<td>35</td>
<td><strong>Guidance on Managing Neurologic Toxicities for TECARTUS</strong>&lt;br&gt;Grading and Management of TECARTUS-Related Neurologic Toxicities (continued)&lt;br&gt;[Grading and Management Table – per the YESCARTA and TECARTUS Adverse Reaction Management Guide for Grade 3 and Grade 4]</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td><strong>Adverse Event Reporting</strong>&lt;br&gt;Reporting suspected adverse events after administration of therapy is important. It allows continued monitoring of the risk/benefit balance of therapy.&lt;br&gt;<em><em>Hospitals and their associated clinics must report any serious adverse event</em> suggestive of CRS or neurologic toxicities to Kite at 1-844-454-KITE (5483) or <a href="mailto:medinfo@kitepharma.com">medinfo@kitepharma.com</a> or <a href="http://www.Gilead.com">www.Gilead.com</a> or FDA at 1-800-FDA-1088 or <a href="http://www.fda.gov/medwatch">www.fda.gov/medwatch</a>. Healthcare providers are also encouraged to report any suspected serious adverse events</em> associated with YESCARTA or TECARTUS as outlined above.**&lt;br&gt;* 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</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td><strong>Patient Counseling</strong>&lt;br&gt;• Talk to the patient about the risk of CRS and neurologic toxicities. Tell them to contact their healthcare provider</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td><strong>Patient Counseling</strong>&lt;br&gt;• Talk to the patient about the risk of CRS and neurologic toxicities. Tell them to contact their healthcare provider</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
and/or seek immediate care if experiencing the signs and symptoms associated with CRS and neurologic toxicities:
- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Chills or shaking chills
- Confusion
- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heartbeat
- Severe fatigue or weakness

• Provide the YESCARTA and TECARTUS REMS Patient Wallet Card to the patient or the patient’s caregiver. Tell the patient to carry the Patient Wallet Card at all times and to share the Patient Wallet Card with any healthcare provider involved in the patient's treatment.
• Advise patients to refrain from driving or operating heavy or potentially dangerous machinery until at least 8 weeks after YESCARTA or TECARTUS infusion

Instruct patient to remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following YESCARTA or TECARTUS infusion.

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<tr>
<th>Slide Number (Current)</th>
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</thead>
<tbody>
<tr>
<td>40</td>
<td>YESCARTA and TECARTUS REMS Program Resources</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>
| 41                     | YESCARTA and TECARTUS REMS Program Kit Includes:  
  • YESCARTA full Prescribing Information and Medication Guide
  • TECARTUS full Prescribing Information and Medication Guide
  • YESCARTA and TESCARTUS REMS Program Training
  • YESCARTA and TECARTUS REMS Program Knowledge Assessment | N/A |                           |
### Additional YESCARTA and TECARTUS REMS Program Information and Resources

To enroll in the YESCARTA and TECARTUS REMS Program or obtain information regarding enrollment in the program, call 1-844-454-KITE or visit the YESCARTA and TECARTUS REMS Program website at www.YescartaTecartusREMS.com. The REMS Program website contains the most current version of REMS-related materials.

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This follow-up guidance is supplemental to the Yescarta® US Prescribing Information (USPI).

Guidance on Managing Cytokine Release Syndrome (CRS)

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in the table below. 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 cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

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>If symptoms (e.g., fever) not improving after 24 hours, consider managing as Grade 2.</td>
<td>If not improving after 3 days, administer one dose of dexamethasone 10 mg intravenously.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. If improving, discontinue tocilizumab.</td>
<td>Administer dexamethasone 10 mg intravenously once daily. If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.</td>
</tr>
<tr>
<td>CRS Grade*</td>
<td>Tocilizumab</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Per Grade 2.</td>
<td>Dexamethasone 10 mg intravenously three times a day.</td>
</tr>
<tr>
<td>Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO₂ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.</td>
<td>If improving, manage as appropriate grade above.</td>
<td>If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate.</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Per Grade 2.</td>
<td>Administer methylprednisolone 1000 mg intravenously once per day for 3 days.</td>
</tr>
<tr>
<td>Life-threatening symptoms. Requirements for ventilator support, continuous venovenous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis).</td>
<td>If improving, manage as appropriate grade above.</td>
<td>If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate.</td>
</tr>
<tr>
<td>If not improving, manage as Grade 4.</td>
<td></td>
<td>If not improving, consider methylprednisolone 1000 mg 2-3 times a day or alternate therapy.†</td>
</tr>
</tbody>
</table>

*Lee et al. 2014.
†Refer to page 2 for management of neurologic toxicity.
‡Refer to tocilizumab Prescribing Information for details.
†Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.
**Guidance on Managing Neurologic Toxicity**

Monitor patients for signs and symptoms of neurologic toxicity/immune effector cell-associated neurotoxicity syndrome (ICANS). Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities/ICANS should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Consider levetiracetam for seizure prophylaxis for any grade of neurologic toxicities.

**Neurologic Toxicity/ICANS Grading and Management Guidance**

<table>
<thead>
<tr>
<th>Neurologic Event*</th>
<th>Concurrent CRS</th>
<th>No Concurrent CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples include:</td>
<td>Administer tocilizumab per the table on page 1 for management of Grade 1 CRS.</td>
<td>Administer one dose of dexamethasone 10 mg intravenously.</td>
</tr>
<tr>
<td>Somnolence—mild drowsiness or sleepiness</td>
<td>In addition, administer one dose of dexamethasone 10 mg intravenously.</td>
<td>If not improving after 2 days, repeat dexamethasone 10 mg intravenously.</td>
</tr>
<tr>
<td>Confusion—mild disorientation</td>
<td>If not improving after 2 days, repeat dexamethasone 10 mg intravenously.</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy—mild limiting of ADLs</td>
<td>Consider levetiracetam for seizure prophylaxis.</td>
<td></td>
</tr>
<tr>
<td>Dysphasia—not impairing ability to communicate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples include:</td>
<td>Administer tocilizumab per the table on page 1 for management of Grade 2 CRS.</td>
<td>Administer dexamethasone 10 mg intravenously four times a day.</td>
</tr>
<tr>
<td>Somnolence—moderate, limiting instrumental ADLs</td>
<td>In addition, administer dexamethasone 10 mg intravenously four times a day.</td>
<td>If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate.</td>
</tr>
<tr>
<td>Confusion—moderate disorientation</td>
<td>If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate.</td>
<td>If not improving, manage as appropriate grade below.</td>
</tr>
<tr>
<td>Encephalopathy—limiting instrumental ADLs</td>
<td>If not improving, manage as appropriate grade below.</td>
<td></td>
</tr>
<tr>
<td>Dysphasia—moderate impairing ability to communicate spontaneously</td>
<td>Consider levetiracetam for seizure prophylaxis.</td>
<td></td>
</tr>
<tr>
<td>Seizure(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic Event*</td>
<td>Concurrent CRS</td>
<td>No Concurrent CRS</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
| **Grade 3**  
Examples include: Somnolence—obtundation or stupor  
Confusion—severe disorientation  
Encephalopathy—limiting self-care ADLs  
Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly | Administer tocilizumab per the table on page 1 for management of Grade 2 CRS.  
In addition, administer methylprednisolone 1000 mg intravenously once daily.  
If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate.  
If not improving, manage as Grade 4. | Administer methylprednisolone 1000 mg intravenously once daily.  
If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate.  
If not improving, manage as Grade 4. |
| **Grade 4**  
Life-threatening consequences  
Urgent intervention indicated  
Requirement for mechanical ventilation  
Consider cerebral edema | Administer tocilizumab per the table on page 1 for management of Grade 2 CRS.  
In addition, administer methylprednisolone 1000 mg intravenously twice per day.  
If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate.  
If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.** | Administer methylprednisolone 1000 mg intravenously twice per day.  
If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate.  
If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.** |

Abbreviation: ADLs, activities of daily living.
*Severity based on Common Terminology Criteria for Adverse Events.
**Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.
**Guidance on Managing Cytokine Release Syndrome (CRS)**

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in the table below. 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 cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive care supportive therapy.

**CRS Grading and Management Guidance**

<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).</td>
<td>If not improving after 24 hours, administer tocilizumab(^1) 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO(_2) or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity.(^1)</td>
<td>Administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS. If improving, discontinue tocilizumab.</td>
</tr>
<tr>
<td>CRS Grade*</td>
<td>Tocilizumab</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>------------</td>
<td>-------------</td>
<td>-----------------</td>
</tr>
<tr>
<td><strong>Grade 3</strong>&lt;br&gt;Symptoms require and respond to aggressive intervention.&lt;br&gt;Oxygen requirement greater than or equal to 40% FiO₂ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.</td>
<td>Per Grade 2&lt;br&gt;If improving, discontinue tocilizumab.</td>
<td>Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids.&lt;br&gt;&lt;br&gt;If improving, manage as Grade 2.&lt;br&gt;&lt;br&gt;If not improving, manage as Grade 4.</td>
</tr>
<tr>
<td><strong>Grade 4</strong>&lt;br&gt;Life-threatening symptoms.&lt;br&gt;Requirements for ventilator support or continuous venovenous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis).</td>
<td>Per Grade 2&lt;br&gt;If improving, discontinue tocilizumab.</td>
<td>Administer methylprednisolone 1000 mg intravenously per day for 3 days.&lt;br&gt;&lt;br&gt;If improving, taper corticosteroids, and manage as Grade 3.&lt;br&gt;&lt;br&gt;If not improving, consider alternate immunosuppressants.</td>
</tr>
</tbody>
</table>

*Lee et al. 2014.<br>†Refer to page 4 for management of neurologic toxicity.<br>‡Refer to tocilizumab Prescribing Information for details.
**Guidance on Managing Neurologic Toxicity**

Monitor patients for signs and symptoms of neurologic toxicities. Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities. Consider non-sedating anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

**Neurologic Toxicity Grading and Management Guidance**

<table>
<thead>
<tr>
<th>Neurologic Event*</th>
<th>Concurrent CRS</th>
<th>No Concurrent CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td></td>
<td>Supportive care.</td>
</tr>
<tr>
<td>Examples include:</td>
<td>Administer tocilizumab per the table on page 3 for management of Grade 1 CRS.</td>
<td></td>
</tr>
<tr>
<td>Somnolence—mild drowsiness or sleepiness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confusion—mild disorientation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy—mild limiting of ADLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphasia—not impairing ability to communicate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Administer tocilizumab per the table on page 3 for management of Grade 2 CRS.</td>
<td>Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less.</td>
</tr>
<tr>
<td>Examples include:</td>
<td>If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids.</td>
<td>If improving, taper corticosteroids.</td>
</tr>
<tr>
<td>Somnolence—moderate, limiting instrumental ADLs</td>
<td>If improving, discontinue tocilizumab.</td>
<td></td>
</tr>
<tr>
<td>Confusion—moderate disorientation</td>
<td>If still not improving, manage as Grade 3.</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy—limiting instrumental ADLs</td>
<td>Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td>
<td></td>
</tr>
<tr>
<td>Neurologic Event*</td>
<td>Concurrent CRS</td>
<td>No Concurrent CRS</td>
</tr>
<tr>
<td>-------------------</td>
<td>----------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples include:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence—obtundation or stupor</td>
<td>Administer tocilizumab per the table on page 3 for management of Grade 2 CRS.</td>
<td>Administer dexamethasone 10 mg intravenously every 6 hours.</td>
</tr>
<tr>
<td>Confusion—severe disorientation</td>
<td>In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids.</td>
<td>Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids.</td>
</tr>
<tr>
<td>Encephalopathy—limiting self-care ADLs</td>
<td>If improving, discontinue tocilizumab and manage as Grade 2.</td>
<td>If not improving, manage as Grade 4.</td>
</tr>
<tr>
<td>Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly</td>
<td>If still not improving, manage as Grade 4.</td>
<td>Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.</td>
</tr>
</tbody>
</table>

| **Grade 4**       |                |                  |
| Life-threatening consequences | Administer tocilizumab per the table on page 3 for management of Grade 2 CRS. | Administer methylprednisolone 1000 mg intravenously per day for 3 days. |
| Urgent intervention indicated | Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. | If improving, then manage as Grade 3. |
| Requirement for mechanical ventilation | If improving, then manage as Grade 3. | If not improving, consider alternate immunosuppressants. |
| Consider cerebral edema | If not improving, consider alternate immunosuppressants. | Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. |

Abbreviation: ADLs, activities of daily living.

*Severity based on Common Terminology Criteria for Adverse Events.

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RISK EVALUATION AND MITIGATION STRATEGY (REMS) DOCUMENT

YESCARTA (axicabtagene ciloleucel) and TECARTUS (brexucabtagene autoleucel) REMS Program

I. Administrative Information

Application Number: BLA 125643 and BLA 125703
Application Holder: Kite Pharma, Inc.
Initial REMS Approval: 07/2020
Most Recent REMS Update: 01/2022

II. REMS Goals

The goals of the YESCARTA and TECARTUS 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 YESCARTA and/or TECARTUS are specially certified and have on-site, immediate access to tocilizumab.

2. Ensuring those who prescribe, dispense, or administer YESCARTA and/or TECARTUS are aware of how to manage the risks of CRS and neurological toxicities.
### III. REMS Requirements

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

1. **Hospitals and their associated clinics that dispense YESCARTA and/or TECARTUS must:**

   | To become certified to dispense | 1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours). |
   |  | 2. Designate an authorized representative to complete the certification process and oversee implementation and compliance with the REMS Program requirements on behalf of the hospital and its associated clinics. |
   |  | 3. Have the authorized representative enroll in the REMS by completing the Hospital Enrollment Form and submitting it to the REMS Program. |
   |  | 4. Have the authorized representative complete the Program Training. |
   |  | 5. Have the authorized representative successfully complete a Knowledge Assessment and submit it to the REMS Program. |
   |  | 6. Train all relevant staff involved in prescribing, dispensing, or administering of YESCARTA and/or TECARTUS on the REMS Program requirements using the Program Training and Adverse Reaction Management Guide. |
   |  | 7. Have all relevant staff involved in prescribing, dispensing, or administering YESCARTA and/or TECARTUS successfully complete the Knowledge Assessment. |
   |  | 8. Establish processes and procedures to ensure relevant new staff involved in prescribing, dispensing, or administering YESCARTA and/or TECARTUS are trained and complete the Knowledge Assessment. |
   |  | 9. 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). |
   |  | 10. Establish processes and procedures to provide patients with the Patient Wallet Card. |
   |
   | Before infusion | 11. 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. |
1. **Hospitals and their associated clinics that dispense YESCARTA and/or TECARTUS must:**

<table>
<thead>
<tr>
<th>Before discharge</th>
<th>12. Provide the patient with the <a href="#">Patient Wallet Card</a> through the processes and procedures established as a requirement of the REMS Program.</th>
</tr>
</thead>
<tbody>
<tr>
<td>To maintain certification to dispense, if there is a change in authorized representative</td>
<td>13. Have the new authorized representative enroll in the REMS Program by completing the <a href="#">Hospital Enrollment Form</a>.</td>
</tr>
</tbody>
</table>
| To maintain certification to dispense, if YESCARTA or TECARTUS has not been dispensed at least once annually from the date of initial certification in the REMS Program | 14. Train all relevant staff involved in prescribing, dispensing, or administering YESCARTA and/or TECARTUS on the REMS Program requirements using the [Program Training](#).  
15. Have all relevant staff involved in prescribing, dispensing, or administering YESCARTA and/or TECARTUS successfully complete the [Knowledge Assessment](#). |
| At all times | 16. Report any serious adverse events\(^1\) suggestive of cytokine release syndrome or neurological toxicities to the REMS Program.  
17. Maintain records of staff training.  
18. Maintain documentation that all processes and procedures are in place and are being followed.  
19. Comply with audits by Kite Pharma, Inc. or a third party acting on behalf of Kite Pharma, Inc. to ensure that all training, processes, and procedures are in place and are being followed. |

2. **Patients who are dispensed YESCARTA or TECARTUS:**

| Before discharge | 1. Receive the [Patient Wallet Card](#). |

---

\(^1\) 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.
Kite Pharma, Inc. must provide training to relevant staff who prescribe, dispense, or administer YESCARTA and/or TECARTUS.

The training includes the following educational material: Program Training. The Training must be provided in-person, live webcast, or on-line.

**To support REMS Program operations, Kite Pharma, Inc. must:**

1. Ensure that YESCARTA and TECARTUS are distributed only to certified hospitals and their associated clinics.
2. Establish and maintain a REMS Program website (www.YescartaTecartusREMS.com). The REMS Program website must include the capability to complete training online, maintain records of that training, and the option to print the Prescribing Information, Medication Guides, and REMS materials. The 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 the website and call center.
4. Establish and maintain a REMS Program call center for REMS participants at 1-844-454-KITE (5483).
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
6. Ensure that hospitals and their associated clinics are able to enroll in the REMS Program in-person, via email, and fax.
7. Notify hospitals and their associated clinics within 7 calendar days after they become certified by the REMS Program.

**To ensure REMS participants’ compliance with the REMS Program, Kite Pharma, Inc. must:**

8. Verify annually that the designated authorized representative remains the same. If different, the hospital and its 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: YESCARTA and/or TECARTUS 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 Program are being met. Take corrective action if noncompliance is identified, including decertification.
11. Maintain an ongoing annual audit plan of hospitals and their associated clinics.
12. Audit all certified hospitals within 180 calendar days from the first order of YESCARTA and/or TECARTUS for the first patient to ensure that all processes and procedures are in place and functioning to support the requirements of the YESCARTA and TECARTUS REMS Program. Certified hospitals and their associated clinics must also be included in the Kite Pharma, Inc. ongoing annual audit plan.
13. Take reasonable steps to improve implementation of and compliance with the requirements in the YESCARTA and TECARTUS REMS Program based on the monitoring and evaluation of the YESCARTA and TECARTUS REMS program.
IV. REMS Assessment Timetable

Kite Pharma, 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 YESCARTA and TECARTUS REMS (07/24/2020). 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 days before the submission date for that assessment. Kite Pharma, 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 YESCARTA and TECARTUS REMS:

Enrollment Forms

   Prescriber:
       1. Hospital Enrollment Form

Training and Educational Materials

   Patient:
       2. Patient Wallet Card

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

Other Materials

   6. REMS Program website
YESCARTA and TECARTUS REMS Program Hospital Enrollment Form

YESCARTA and TECARTUS REMS Program Hospital Enrollment

YESCARTA® and TECARTUS® are available only through the YESCARTA and TECARTUS REMS Program. Only hospitals and their associated clinics certified in the YESCARTA and TECARTUS REMS Program are permitted to dispense YESCARTA and TECARTUS.

YESCARTA and TECARTUS REMS Hospital Attestations

As a condition of certification, the certified hospital and its associated clinics must:

- Ensure that if the hospital and its associated clinics designate a new authorized representative, the new authorized representative must review the YESCARTA and TECARTUS REMS Program Training, complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment, complete a new YESCARTA and TECARTUS REMS Program Hospital Enrollment Form, and submit the forms via fax to 1-310-496-0397 or email at YTREMS@kitepharma.com.

- Report any serious adverse events suggestive of CRS or neurological toxicities.

- Report suspected serious adverse events associated with either YESCARTA or TECARTUS by contacting Kite at 1-844-454-KITE (5483) or medinfo@kitepharma.com or www.Gilead.com or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- Dispense YESCARTA or TECARTUS to patients only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).

- Provide the patient with the Patient Wallet Card.

- Maintain documentation of all processes and procedures for the YESCARTA and TECARTUS REMS Program and provide documentation upon request to Kite, or a third party acting on behalf of Kite.

- Comply with audits by Kite, or a third party acting on behalf of Kite.

YESCARTA and TECARTUS REMS Program Hospital Registration Form

Please email the completed form to YTREMS@kitepharma.com, fax to 1-310-496-0397, or complete it online at www.KiteREMSTraining.com.

Important Notice: Completion of the enrollment form and knowledge assessment does not guarantee that your hospital and its associated clinics will be certified to administer YESCARTA or TECARTUS. Please contact 1-844-454-KITE or visit the YESCARTA and TECARTUS REMS Program website at www.YescartaTecartusREMS.com for more information.

YESCARTA and TECARTUS REMS Program Hospital Enrollment Form

To finalize your registration in the YESCARTA and TECARTUS REMS Program, please complete the form below in its entirety if not being submitted online.
Authorized Representative Information:

First Name: _____________________________________ Last Name: _____________________________________

Title: ___________________ Credentials: ☐ DO ☐ MD ☐ RPh ☐ RN ☐ NP/PA ☐ Other: ________________________

Phone Number: ___________________________ Fax Number: ___________________________

Email Address: _____________________________________________

Hospital/ Associated Clinic Contact Information:

Hospital/ Associated Clinic Name: _________________________________________________________________

Street Address: ______________________________________________________________________________

City: _______________________________________ State: _____________________ ZIP Code: ____________

YESCARTA and TECARTUS REMS Authorized Representative Attestations

• I am the authorized representative designated by my hospital and its associated clinics to coordinate the activities of the YESCARTA and TECARTUS REMS Program.

• By signing this form, I attest that I understand and agree to comply with the following REMS Program requirements:

• I must complete the YESCARTA and TECARTUS REMS Program Training and successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment.

• I must submit this completed YESCARTA and TECARTUS REMS Program Hospital Enrollment Form to Kite via fax at 1-310-496-0397, email to YTREMS@kitepharma.com, or online at www.KiteREMSTraining.com.

• I must submit the YESCARTA and TECARTUS REMS Program Knowledge Assessment online on the REMS Program Training website or send to Kite via fax at 1-310-496-0397 or email to YTREMS@kitepharma.com.

• I will oversee implementation and compliance with the YESCARTA and TECARTUS REMS Program.
• I will ensure that my hospital and its associated clinics establishes processes and procedures that are subject to monitoring by Kite or a third party acting on behalf of Kite to help ensure compliance with the requirements of the YESCARTA and TECARTUS REMS Program, including the following, before administering YESCARTA or TECARTUS:
  
o  Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA or TECARTUS are trained on the YESCARTA and TECARTUS REMS Program requirements as described in the training materials, successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment, and maintain training records for all staff.
  
o  Put processes and procedures in place to ensure that relevant staff involved in the prescribing, dispensing, or administering of YESCARTA or TECARTUS are retrained if YESCARTA or TECARTUS have not been dispensed at least once annually from the date of certification in the YESCARTA and TECARTUS REMS Program.
  
o  Prior to dispensing YESCARTA or TECARTUS, put processes and procedures in place to verify a minimum of 2 doses of tocilizumab are available on-site for each patient and are ready for immediate administration (within 2 hours).
  
o  Prior to discharge, provide patients/caregivers with the Patient Wallet Card and instruct patient to remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following YESCARTA or TECARTUS infusion.

Authorized Representative Name

Title

Signature

Date

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患者信息

YESCARTA®和TECARTUS®可引起可能导致死亡的副作用。

如果您出现以下任何症状，请立即致电或去看您的肿瘤科医生或寻求紧急帮助：

- 发热（100.4°F/38°C 或更高）
- 眩晕或头晕
- 呼吸困难
- 呕吐或腹泻
- 发冷或寒战
- 意识模糊
- 重度恶心
- 心跳加快或不规则
- 重度疲乏或虚弱

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患者钱包卡

随身携带这张卡片。如果您去急诊室或看任何医生，请出示此卡。

告知任何为您看诊的医务人员您正在接受 YESCARTA®或 TECARTUS®治疗。

服用 YESCARTA®或 TECARTUS®后，在您接受治疗的地点周围（2小时车程内）停留至少4周。
医务人员的重要信息

治疗肿瘤学家姓名：

工作时间电话：

非工作时间电话：

Kite CAR T 产品给药：
- YESCARTA®
- TECARTUS®

Kite CAR T 输注日期：

- 该患者接受了 CD19 导向的转基因自体 T 细胞免疫治疗（CAR T）。

- CAR T 治疗可引起细胞因子释放综合征（CRS）和神经毒性，可能致命或危及生命。CRS 可能涉及任何器官系统

- 请立即联系患者的肿瘤科医生以获得更多信息

请访问 www.yescartatecartusrems.com 获取更多信息。
Patient Information

YESCARTA® and TECARTUS® can cause side effects that can lead to death. Call or see your oncologist or get emergency help RIGHT AWAY if you have any of these symptoms:

- Fever (100.4°F/38°C or higher)
- Difficulty breathing
- Chills or shaking chills
- Confusion

- Dizziness or lightheadedness
- Severe nausea, vomiting, or diarrhea
- Fast or irregular heartbeat
- Severe fatigue or weakness

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Patient Wallet Card

Carry this card with you at all times. SHOW THIS CARD if you go to the emergency room or see any physician.

Tell any healthcare provider that sees you that you are being treated with YESCARTA® or TECARTUS®.

Stay within close proximity (within 2 hours) of the location where you received your treatment for at least 4 weeks after getting YESCARTA® or TECARTUS®.
Important Information for Healthcare Providers

Name of treating oncologist: ________________________________

Office phone: ________________________________

After-hours phone: ________________________________

Kite CAR T product administered:
☐ YESCARTA®
☐ TECARTUS®

Date of Kite CAR T infusion: ________________________________

- This patient has received a CD19-directed genetically modified autologous T-cell immunotherapy (CAR T).

- CAR T therapy can cause cytokine release syndrome (CRS) and neurologic toxicities, which may be fatal or life threatening. CRS may involve any organ system.

- Contact the patient’s oncologist immediately for further information.

For more information, please visit www.yescartatecartusrems.com.
Información para el paciente

YESCARTA® y TECARTUS® pueden causar efectos secundarios que pueden provocar la muerte.

Llame o consulte a su oncólogo o busque ayuda de urgencia DE INMEDIATO si tiene alguno de estos síntomas:

- Fiebre (100.4 °F/38 °C o más)
- Dificultad para respirar
- Escalofríos o temblores
- Confusión
- Mareo
- Náuseas, vómitos o diarrea intensos
- Latido cardíaco rápido o irregular
- Fatiga o debilidad intensa

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GILEAD es una marca comercial de Gilead Sciences, Inc.

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Tarjeta de bolsillo del paciente

Lleve esta tarjeta con usted en todo momento. MUESTRE ESTA TARJETA si va a un servicio de urgencias o si consulta a un médico.

Informe al profesional sanitario que lo vea que está siendo tratado con YESCARTA® o TECARTUS®.

Permanezca muy cerca (a una distancia máxima de 2 horas) del lugar en el que recibió el tratamiento durante, al menos, 4 semanas después de recibir YESCARTA® o TECARTUS®.
Información importante para profesionales sanitarios

Nombre del oncólogo tratante: ________________________________

Teléfono del consultorio: ________________________________

Teléfono después del horario de atención: ________________________________

Medicamento T-CAR de Kite que se administró:
☐ YESCARTA®
☐ TECARTUS®

Fecha de la infusión T-CAR de Kite: ________________________________

- Este paciente ha recibido una inmunoterapia con linfocitos T (T-CAR) autólogos, modificados genéticamente y dirigidos a CD19.

- La terapia con T-CAR puede causar síndrome de liberación de citocinas (SLC) y efectos secundarios neurológicos, que pueden ser mortales o potencialmente mortales. El SLC puede afectar a cualquier aparato y sistema.

- Comuníquese de inmediato con el oncólogo del paciente para obtener más información.

Visite www.yescartatecartusrems.com para obtener más información.
What Is the YESCARTA and TECARTUS REMS Program?

A REMS is a program required by the United States (US) Food and Drug Administration (FDA). The FDA has determined that a REMS is necessary to ensure that the benefits of YESCARTA and TECARTUS outweigh the risks of cytokine release syndrome and neurologic toxicities. YESCARTA and TECARTUS are available only through the YESCARTA and TECARTUS REMS Program.

Boxed Warning for YESCARTA

Cytokine Release Syndrome

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with YESCARTA
- CRS occurred in 90% (379/422) of patients with non-Hodgkin lymphoma (NHL) receiving YESCARTA, including ≥ Grade 3 CRS in 9%
- CRS occurred in 93% (256/276) of patients with large B-cell lymphoma (LBCL), including ≥ Grade 3 CRS in 9%
- CRS occurred in 84% (123/146) of patients with indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5, including ≥ Grade 3 CRS in 8%
- For patients with LBCL, the median time to onset of CRS in:
  - ZUMA-1 was 2 days following infusion (range: 1-12 days)
  - ZUMA-7 was 3 days following infusion (range: 1-10 days)
- For patients with iNHL, the median time to onset of CRS was 4 days (range: 1-20 days)
- For patients with LBCL, the median duration of CRS in:
  - ZUMA-1 was 7 days (range: 2-58 days)
  - ZUMA-7 was 7 days (range: 2-43 days)
For patients with iNHL the median duration of CRS was 6 days (range: 1-27 days)

- 45% (49/108) of patients with LBCL in ZUMA-1, and 67% (112/168) of patients with LBCL in ZUMA-7 received tocilizumab after infusion of YESCARTA
- 51% (75/146) of patients with iNHL received tocilizumab after infusion of YESCARTA
- Among patients who died after receiving YESCARTA, 4 patients with LBCL and 1 patient with iNHL had ongoing CRS events at the time of death
- Key manifestations of CRS (≥10%) in all patients combined include fever (85%), hypotension (40%), tachycardia (32%), chills (22%), hypoxia (20%), headache (15%), and fatigue (12%)
- Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), renal insufficiency, cardiac failure, respiratory failure, cardiac arrest, capillary leak syndrome, multi-organ failure, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
- The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of CRS was assessed in two subsequent cohorts of LBCL patients (ZUMA-1).

Among patients who received tocilizumab and/or corticosteroids for ongoing Grade 1 events:
- CRS occurred in 93% (38/41) including 2% (1/41) with Grade 3 CRS; no patients experienced a Grade 4 or 5 event
- The median time to onset of CRS was 2 days (range: 1-8 days)
- The median duration of CRS was 7 days (range: 2-16 days)

Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA:
- Thirty-one out of 39 patients (79%) developed CRS with no patients developing Grade 3 or higher CRS
- The median time to onset of CRS was 5 days (range: 1-15 days)
- The median duration of CRS was 4 days (range: 1-10 days)
- Although there is no known mechanistic explanation, consider the risk and benefits of prophylactic corticosteroids in the context of pre-existing comorbidities for the individual patient and the potential for the risk of Grade 4 and prolonged neurologic toxicities

**Neurologic Toxicities**

- Neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome (ICANS)) that were fatal or life-threatening occurred following treatment with YESCARTA
• Neurologic toxicities occurred in 78% (330/422) of patients with NHL receiving YESCARTA, including ≥ Grade 3 cases in 25%
• Neurologic toxicities occurred in 87% (94/108) of patients with LBCL in ZUMA-1, including ≥ Grade 3 cases in 31% and in 74% (124/168) of patients in ZUMA-7 including ≥ Grade 3 cases in 25%
• Neurologic toxicities occurred in 77% (112/146) of patients with iNHL, including ≥ Grade 3 in 21%
• Neurologic toxicities occurred within the first 7 days of YESCARTA infusion for 87% of affected patients with LBCL and 74% of affected patients with iNHL
• For patients with LBCL, the median time to onset of neurologic toxicities in:
  o ZUMA-1 was 4 days (range: 1-43 days)
  o ZUMA-7 was 5 days (range: 1-133 days)
For patients with iNHL, the median time to onset of neurologic toxicities was 6 days (range: 1-79 days)
• For patient with LBCL, the median duration of neurologic toxicities in:
  o ZUMA-1 was 17 days
  o ZUMA-7 was 15 days
For patients with iNHL, the median duration was 16 days
• The most common neurologic toxicities (≥10%) in all patients combined included encephalopathy (50%), headache (43%), tremor (29%), dizziness (21%), aphasia (17%), delirium (15%), and insomnia (10%)
• Prolonged encephalopathy lasting up to 173 days was noted
• Serious events including aphasia, leukoencephalopathy, dysarthria, lethargy, and seizures occurred in patients treated with YESCARTA
• Fatal and serious cases of cerebral edema and encephalopathy, including late-onset encephalopathy, have occurred in patients treated with YESCARTA
• The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of neurologic toxicities was assessed in two subsequent cohorts of LBCL patients (ZUMA-1)
  Among patients who received corticosteroids at the onset of Grade 1 toxicities:
  o Neurologic toxicities occurred in 78% (32/41) and 20% (8/41) had Grade 3 neurologic toxicities; no patients experienced a Grade 4 or Grade 5 event
  o The median time to onset of neurologic toxicities was 6 days (range: 1-93 days)
  o The median duration was 8 days (range: 1-144 days)
Prophylactic treatment with corticosteroids was administered to a cohort of 39 patients for 3 days beginning on the day of infusion of YESCARTA:
  o Thirty-three out of the 39 patients (85%) developed neurologic toxicities and 8% (3/39) developed Grade 3 and 5% (2/39) developed Grade 4 neurologic toxicities
The median time to onset of neurologic toxicities was 6 days (range: 1-274 days)

The median duration of 12 days (range: 1-107 days)

Prophylactic corticosteroids for management of CRS and neurologic toxicities may result in higher grade of neurologic toxicities or prolongation of neurologic toxicities, delay the onset and decrease the duration of CRS

Boxed Warning for TECARTUS

Cytokine Release Syndrome

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with TECARTUS
- CRS occurred in 91% (75/82) of patients with MCL, including ≥ Grade 3 (Lee grading system) CRS in 18% of patients. CRS occurred in 92% (72/78) of patients with ALL, including ≥ Grade 3 (Lee grading system) CRS in 26% of patients
- Among the patients with MCL who died after receiving TECARTUS, one had a fatal CRS event. Three patients with ALL had ongoing CRS events at the time of death
- The median time to onset of CRS was 3 days (range: 1-13 days), and the median duration of CRS was 10 days (range: 1-50 days) for patients with MCL. The median time to onset of CRS was 5 days (range: 1-12 days) and the median duration of CRS was 8 days (range: 2-63 days) for patients with ALL
- Key manifestations of CRS (>10%) were similar in MCL and ALL and included fever (93%), hypotension (62%), tachycardia (59%), chills (32%), hypoxia (31%), headache (21%), fatigue (20%), and nausea (13%)
- Serious events associated with CRS in MCL and ALL combined (≥2%) included hypotension, fever, hypoxia, tachycardia, and dyspnea


Neurologic Toxicities

- Neurologic events, including those that were fatal or life-threatening, occurred following treatment with TECARTUS
- The median time to onset for neurologic events was 6 days (range: 1-32 days) with a median duration of 21 days (range: 2-454 days) in patients with MCL. The median time to onset for neurologic events was 7 days (range: 1-51 days) with a median duration of 15 days (range: 1-397 days) in patients with ALL
Neurologic events occurred in 81% (66/82) of patients with MCL, including ≥ Grade 3 in 37% of patients. Neurologic events occurred in 87% (68/78) of patients with ALL, including ≥ Grade 3 in 35% of patients.

Nine patients (3 patients with MCL and 6 patients with ALL) had ongoing neurologic events at the time of death.

Neurologic events resolved for 119 out of 134 (89%) of all patients treated with TECARTUS.

Ninety-one percent of all treated patients experienced the first CRS or neurological event within the first 7 days after TECARTUS infusion.

The most common neurologic events (>10%) were similar in MCL and ALL and included encephalopathy (57%), headache (37%), tremor (34%), confusional state (26%), aphasia (23%), delirium (17%), dizziness (15%), anxiety (14%), and agitation (12%).

Serious events (≥ 2%) including encephalopathy, aphasia, confusional state, and seizures occurred after treatment with TECARTUS.

**YESCARTA and TECARTUS REMS Program Requirements**

Hospitals and their associated clinics must be enrolled in the YESCARTA and TECARTUS REMS Program to be able to dispense YESCARTA and/or TECARTUS.

All relevant staff involved in the prescribing, dispensing, or administering of YESCARTA and/or TECARTUS are trained on the YESCARTA and TECARTUS REMS Program requirements, and must successfully complete a YESCARTA and TECARTUS REMS Program Knowledge Assessment.

**Hospital Enrollment Instructions**

An authorized representative must enroll in the YESCARTA and TECARTUS REMS Program on behalf of the hospital and its associated clinics. To be enrolled in the YESCARTA and TECARTUS REMS Program, the representative must:

1. Complete the training program, which includes review of:

   - YESCARTA and TECARTUS full Prescribing Information
   - YESCARTA and TECARTUS REMS Program Training
   - YESCARTA and TECARTUS Adverse Reaction Management Guide

   - Successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment.
• Complete the YESCARTA and TECARTUS REMS Program Hospital Enrollment Form.
• Oversee implementation and compliance with the YESCARTA and TECARTUS REMS Program requirements:
  • Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA and/or TECARTUS are trained on the REMS Program requirements and successfully complete the YESCARTA and TECARTUS REMS Program Knowledge Assessment. The authorized representative will determine relevant staff who require training
  • Maintain training records of staff
  • Ensure that the hospital and its associated clinics have a minimum of 2 doses of tocilizumab available on-site for each patient and are ready for immediate administration (within 2 hours)
  • Prior to patient discharge, provide patients/caregivers with the Patient Wallet Card and instruct patient to remain within close proximity (within 2 hours) of the certified administering hospital and its associated clinics for at least 4 weeks following YESCARTA or TECARTUS infusion
  • Put processes and procedures in place to ensure that relevant new staff are trained, and relevant staff are retrained if YESCARTA or TECARTUS has not been dispensed at least once annually from the date of certification in the YESCARTA and TECARTUS REMS Program

**Indication**

YESCARTA is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

• Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.

• Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.

**Limitation of Use:** YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.
• Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Indication
TECARTUS is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of:

• Adult patients with relapsed or refractory mantle cell lymphoma (MCL). This indication is approved under accelerated approval based on overall response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

• Adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

Where to Find YESCARTA and TECARTUS REMS Program Information and Resources
For more information about the YESCARTA and TECARTUS REMS Program, see the Program Resources or call 1-844-454-KITE (5483).

Reporting Adverse Reactions

Hospitals and their associated clinics must report any serious adverse event* suggestive of CRS or neurologic toxicities to Kite at 1-844-454-KITE (5483) or medinfo@kitepharma.com or www.Gilead.com 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 YESCARTA or TECARTUS as outlined 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
Need Help?
If you have questions about the YESCARTA and TECARTUS REMS Program or need help registering, call 1-844-454-KITE.

LEFT HAND CORNER:
Resources for Healthcare Professionals
Download All Resources

YESCARTA and TECARTUS REMS Program Knowledge Assessment
YESCARTA and TECARTUS REMS Program Training
YESCARTA and TECARTUS REMS Program Hospital Enrollment Form
YESCARTA and TECARTUS Adverse Reaction Management Guide

YESCARTA and TECARTUS REMS Training
Log in to the YESCARTA and TECARTUS REMS Learning Management System
[When the end user clicks on this hyperlink, an intermediary page loads which states: Contact your institution’s Authorized Representative for REMS Training. You are now leaving YescartaTecartusREMS.com. Select CANCEL to return or OK to continue.]

Resources for Patients

All patients treated with YESCARTA or TECARTUS receive a Patient Wallet Card listing adverse reactions and other information. Patients should carry the card with them at all times and show it to any healthcare professional who treats them, including in the emergency room. Non-English-speaking patients are given Patient Wallet Cards in both English and their native language. They should carry both versions of the card with them at all times.

YESCARTA and TECARTUS REMS Patient Wallet Card

Chinese       English       Spanish

Adobe Reader is required to view PDFs. If you do not have it installed, download it here.

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