RISK EVALUATION AND MITIGATION STRATEGY (REMS) DOCUMENT

YESCARTA (Axicabtagene Ciloleucel) REMS Program

I. Administrative Information

Application Number: BLA 125643
Application Holder: Kite Pharma, Inc.
Initial REMS Approval: 10/2017
Most Recent REMS Update: XX/2019

II. REMS Goal

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

2. Ensuring those who prescribe, dispense, or administer YESCARTA 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 must:

<table>
<thead>
<tr>
<th>To become certified to dispense</th>
<th>1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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 their associated clinics.</td>
</tr>
<tr>
<td></td>
<td>3. Have the authorized representative enroll in the REMS by completing the Hospital Enrollment Form and submitting it to the REMS Program.</td>
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<td></td>
<td>4. Have the authorized representative complete the Live Training.</td>
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<tr>
<td></td>
<td>5. Have the authorized representative successfully complete a Knowledge Assessment and submit it to the REMS Program.</td>
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<tr>
<td></td>
<td>6. Train all relevant staff involved in prescribing, dispensing, or administering of YESCARTA on the REMS Program requirements using the Live Training and Adverse Reaction Management Guide.</td>
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<tr>
<td></td>
<td>7. Have all relevant staff involved in prescribing, dispensing, or administering of YESCARTA successfully complete the Knowledge Assessment.</td>
</tr>
<tr>
<td></td>
<td>8. Establish processes and procedures to ensure relevant new staff involved in prescribing, dispensing, or administering of YESCARTA are trained and complete the Knowledge Assessment.</td>
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<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>10. Establish processes and procedures to provide patients with the Patient Wallet Card.</td>
</tr>
<tr>
<td>Before infusion</td>
<td>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.</td>
</tr>
<tr>
<td>Before discharge</td>
<td>12. Provide the patient with the Patient Wallet Card through the processes and procedures established as a requirement of the REMS Program.</td>
</tr>
</tbody>
</table>
1. Hospitals and their associated clinics that dispense YESCARTA must:

<table>
<thead>
<tr>
<th>To maintain certification to dispense</th>
<th>13. Have the new authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form.</th>
</tr>
</thead>
<tbody>
<tr>
<td>To maintain certification to dispense, if YESCARTA has not been dispensed at least once annually from the date of initial certification in the REMS Program</td>
<td>14. Train all relevant staff involved in prescribing, dispensing, or administering of YESCARTA on the REMS Program requirements using the Live Training.</td>
</tr>
<tr>
<td>At all times</td>
<td>15. Have all relevant staff involved in prescribing, dispensing, or administering of YESCARTA successfully complete the Knowledge Assessment.</td>
</tr>
<tr>
<td>At all times</td>
<td>16. Report any serious adverse events(^1) suggestive of cytokine release syndrome or neurological toxicities to the REMS Program.</td>
</tr>
<tr>
<td></td>
<td>17. Maintain records of staff training.</td>
</tr>
<tr>
<td></td>
<td>18. Maintain documentation that all processes and procedures are in place and are being followed.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>

2. Patients who are dispensed YESCARTA:

| Before discharge | 1. Receive the Patient Wallet Card. |

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**Kite Pharma, Inc. must provide training to relevant staff who prescribe, dispense, or administer Yescarta.**

The training includes the following educational material: *Live Training*. The Training must be provided in-person or live webcast.

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

1. Ensure that YESCARTA is distributed only to certified hospitals and their associated clinics.

2. Establish and maintain a REMS Program Website (www.YESCARTArems.com). The REMS Program Website must include the option to print the Prescribing Information, Medication Guide, 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.

5. Establish and maintain a validated, secure database of hospitals and their associated clinics that are certified to administer Yescarta in the YESCARTA 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 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: YESCARTA 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 after the hospital places its first order for YESCARTA to ensure that all processes and procedures are in place and functioning to support the requirements of the YESCARTA 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 REMS Program based on the monitoring and evaluation of the YESCARTA 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 REMS (10/18/2017). 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 REMS:

**Enrollment Forms**

Prescriber:

1. Hospital Enrollment Form

**Training and Educational Materials**

Patient:

2. Patient Wallet Card

Healthcare Setting:

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

**Other Materials**

6. REMS Program website
Guidance on Managing Cytokine Release Syndrome (CRS)

Patients should be monitored for signs and symptoms of CRS. Diagnosis of CRS requires ruling out alternate causes of systemic inflammatory response, including concurrent infections. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on YESCARTA®. This includes the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS.

### 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>N/A</td>
</tr>
</tbody>
</table>
| **Grade 2**      | Symptoms require and respond to moderate intervention  
Oxygen requirement less than 40% FiO₂ or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity† | Administer tocilizumab  
8 mg/kg intravenous per 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 | Manage per Grade 2 if no improvement within 24 hours after starting tocilizumab |
| **Grade 3**      | 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 | Per Grade 2 | Administer methylprednisolone  
1 mg/kg intravenous twice daily or equivalent dexamethasone (e.g., 10 mg intravenous every 6 hours)  
Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days |
| **Grade 4**      | Life-threatening symptoms  
Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis) | Per Grade 2 | Administer methylprednisolone  
1000 mg intravenous per day for 3 days; if improves, then manage as above |

†Refer to the table on the back for management of neurologic toxicity.
‡Refer to tocilizumab Prescribing Information for details.

Abbreviation: CVVHD, continuous veno-venous hemodialysis.
## Guidance on Managing Neurologic Toxicity

Monitor patients for signs and symptoms of neurologic toxicities. Treatment algorithms have been developed to ameliorate the neurologic toxicities experienced by patients on YESCARTA®. This includes the use of corticosteroids or corticosteroids and tocilizumab for moderate, severe, or life-threatening neurologic toxicities.

### Neurologic Toxicity Grading and Management Guidance

<table>
<thead>
<tr>
<th>Neurologic Event (Grading Assessment CTCAE 4.03)*</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></td>
<td></td>
</tr>
<tr>
<td>Somnolence—mild drowsiness or sleepiness</td>
<td>Supportive care</td>
<td>Supportive care</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></td>
<td></td>
</tr>
<tr>
<td>Examples include:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence—moderate, limiting instrumental ADLs</td>
<td>Administer tocilizumab per the table on the other side for management of Grade 2 CRS</td>
<td>Administer dexamethasone 10 mg intravenous every 6 hours</td>
</tr>
<tr>
<td>Confusion—moderate disorientation</td>
<td>If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenous every 6 hours if not already taking other corticosteroids</td>
<td>Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days</td>
</tr>
<tr>
<td>Encephalopathy—limiting instrumental ADLs</td>
<td>Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days</td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
</tr>
<tr>
<td>Dysphasia—moderate impairing ability to communicate spontaneously</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure(s)</td>
<td>Administer dexamethasone 10 mg intravenous every 6 hours 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 over 3 days</td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
</tr>
</tbody>
</table>

| **Grade 3**                                      |                |                  |
| Examples include:                                |                |                  |
| Somnolence—obtundation or stupor                 | Administer tocilizumab per the table on the other side for management of Grade 2 CRS | Administer dexamethasone 10 mg intravenous every 6 hours |
| Confusion—severe disorientation                   | In addition, administer dexamethasone 10 mg intravenous 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 over 3 days | Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days |
| Encephalopathy—limiting self-care ADLs           | Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis | Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis |
| Dysphasia—severe receptive or expressive         |                |                  |
| characteristics, impairing ability to read,      |                |                  |
| write, or communicate intelligibly               |                |                  |

| **Grade 4**                                      |                |                  |
| Life-threatening consequences                     | Administer tocilizumab per the table on the other side for management of Grade 2 CRS | Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above |
| Urgent intervention indicated                     | Administer methylprednisolone 1000 mg intravenous per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenous per day for 2 more days; if improves, then manage as above | Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis |
| Requirement for mechanical ventilation            | Consider cerebral edema |                     |
| Consider cerebral edema                           | | |

Abbreviation: ADLs, activities of daily living.

To become an authorized representative for your hospital and its associated clinics in the YESCARTA® 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® REMS Program Knowledge Assessment questions and the YESCARTA® REMS Program Hospital Enrollment Form must be emailed to YESCARTAREMS@kitepharma.com or faxed to 1-310-496-0397.

Questions

1. What is the approved indication for YESCARTA®?
   A. Patients with relapsing multiple sclerosis
   B. Patients with lung cancer
   C. Patients with bladder cancer
   D. 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.

2. Prior to discharge, a YESCARTA® Patient Wallet Card must be given to patients who have been infused with YESCARTA®.
   True ____  False ____

3. 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 CRS, within 2 hours of YESCARTA® infusion.
   True ____  False ____

4. After YESCARTA® infusion, patients should be advised to:
   A. Refrain from driving or operating heavy or potentially dangerous machinery after YESCARTA® administration until at least 8 weeks after 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 neurologic toxicities
   D. All of the above

5. Which of the following is true regarding the time to onset of CRS? It typically occurs:
   A. With a median time to onset of 7 days
   B. With a median time to onset of 5 days
   C. With a median time to onset of 2 days
   D. Rarely starts during the first week following YESCARTA® infusion

Continued on Back
6. All of the following regarding neurologic toxicity related to YESCARTA® 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 days
   D. The most common signs or symptoms of neurologic toxicity include encephalopathy, headache, tremor, dizziness, aphasia, delirium, insomnia, and anxiety

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. Appropriate management for this patient would include (please select single best answer):
   A. Consider nonsedating, antiseizure medicines (e.g., 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 every 6 hours
   D. A and C

8. One day after infusion of YESCARTA®, a 60-year-old man with relapsed diffuse large B-cell lymphoma (DLBCL) develops the following signs and symptoms of CRS: high fever (39°C-40°C), hypoxia requiring <40% FiO₂, and hypotension requiring intravenous fluids. 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 ____________________________

I am the authorized representative  ____ Yes  ____ No

Hospital/Associated Clinic Name  ________________________________

Address _____________________________________________

City ____________________________________________ State ________ ZIP Code ___________

Signature ____________________________________________ Date ____________

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Patient Information

YESCARTA® 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

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

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

Name of treating oncologist: ____________________________

Office phone: ____________________________

After-hours phone: ____________________________

Date of YESCARTA® (axicabtagene ciloleucel) infusion: ____________________________

- This patient has received YESCARTA®, which is a CD19-directed genetically modified autologous T-cell immunotherapy

- YESCARTA® 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
REMS Program Live Training
This educational module contains information on selected YESCARTA®-associated adverse reactions, including cytokine release syndrome and neurologic toxicities. These are not all of the adverse reactions associated with YESCARTA®.
Indication

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

Please see full Prescribing Information, including BOXED WARNING and Medication Guide.
YESCARTA® REMS Program Overview
What Is the YESCARTA® REMS (Risk Evaluation and Mitigation Strategy) Program?

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® is available only under a program called the YESCARTA® REMS Program because of the serious risks of cytokine release syndrome (CRS) and neurologic toxicities.

The goals of the YESCARTA® REMS Program are to mitigate the risks of CRS and neurologic toxicities by:

- Ensuring that hospitals and their associated clinics that dispense YESCARTA® are specially certified and have on-site, immediate access to a minimum of 2 doses of tocilizumab
- Ensuring that those who prescribe, dispense, or administer YESCARTA® are aware of how to manage the risks of CRS and neurologic toxicities
Hospital Certification

To become certified to dispense YESCARTA®, hospitals and their associated clinics must:

1. Designate an authorized representative to complete the training program by completing and submitting the YESCARTA® REMS Program Hospital Enrollment Form on behalf of the hospital and its associated clinics

2. Ensure that the authorized representative oversees implementation and compliance with the YESCARTA® REMS Program requirements

3. Dispense YESCARTA® 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

4. Recertify in the YESCARTA® REMS Program if a new authorized representative is designated
5. Maintain documentation that all processes and procedures are in place and are being followed for the YESCARTA® REMS Program; provide this documentation upon request to Kite, FDA, or a third party acting on behalf of Kite or FDA

6. Comply with audits by Kite, FDA, 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® REMS Program

7. Report any serious adverse events* suggestive of CRS or neurologic toxicities

* 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.
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® REMS Program Hospital Enrollment Form.
YESCARTA® Authorized Representative Attestations

☐ Complete the YESCARTA® REMS Program Live Training and successfully complete the YESCARTA® REMS Program Knowledge Assessment

☐ Submit the completed YESCARTA® REMS Program Hospital Enrollment Form to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com

☐ Submit the YESCARTA® REMS Program Knowledge Assessment to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com

☐ Oversee implementation and compliance with the YESCARTA® REMS Program
YERCARTA® Authorized Representative Attestations (continued)

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 YERCARTA® REMS Program, including the following, before administering YERCARTA®:

- Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YERCARTA® are trained on the REMS Program requirements as described in the training materials, successfully complete the YERCARTA® REMS Program Knowledge Assessment, and maintain training records for all staff.
  - The Authorized Representative will determine relevant staff who require training.
- Put processes and procedures in place to ensure that relevant staff involved in the prescribing, dispensing, or administering of YERCARTA® are retrained if YERCARTA® has not been dispensed at least once annually from the date of certification in the YERCARTA® REMS Program.
- Prior to dispensing YERCARTA®, 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).
- Prior to patient discharge, provide patients/caregivers with the Patient Wallet Card.
Serious Risks of YESCARTA®
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.
Management of CRS
Cytokine Release Syndrome

- CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA®
- In a Kite clinical trial, CRS occurred in 94% (101/108) of patients receiving YESCARTA®, including Grade 3 or higher CRS in 13% (14/108) of patients
- The median time to onset was 2 days (range, 1-12 days)
- The median duration of CRS was 7 days (range, 2-58 days)
- 45% (49/108) of patients received tocilizumab after infusion of YESCARTA®
- Among patients who died after receiving YESCARTA®, 4 had ongoing CRS events at the time of death
Patient Assessment of CRS Associated With Yescarta®

<table>
<thead>
<tr>
<th>The following are signs and symptoms of CRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capillary leak syndrome</td>
</tr>
<tr>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Fever</td>
</tr>
</tbody>
</table>
Guidance on Managing 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 on slide 17
- 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
# Guidance on Management of CRS

## Grading and Management of YESCARTA®-Related CRS

<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>Tocilizumab</th>
<th>Corticosteroids</th>
</tr>
</thead>
</table>
| **Grade 1**
  Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise) | N/A                                                                         | N/A                                 |
| **Grade 2**
  Symptoms require and respond to moderate intervention
  Oxygen requirement less than 40% FiO2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity† | Administer tocilizumab² 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 | Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab |
| **Grade 3**
  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 | Per Grade 2                                                                   |                                     |
  | Per Grade 2                                                                   | Administer methylprednisolone, 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours)
Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days |
| **Grade 4**
  Life-threatening symptoms
  Requirements for ventilator support, CVHD, or Grade 4 organ toxicity (excluding transaminitis) | Per Grade 2                                                                   | Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above |

Abbreviation: CVVHD, continuous veno-venous hemodialysis.


† Refer to the table on slides 22-23 for management of neurologic toxicity.

²Refer to tocilizumab Prescribing Information for details.
Management of Neurologic Toxicities
Neurologic Toxicities

- Neurologic toxicities, that were fatal or life-threatening, occurred following treatment with YESCARTA®
- Neurologic toxicities occurred in 87% of patients, including Grade 3 or higher neurologic toxicities in 31% of patients
- 98% of all neurologic toxicities occurred within the first 8 weeks of YESCARTA® infusion
- The median time to onset was 4 days (range, 1-43 days) following YESCARTA® infusion
- The median duration was 17 days
- Prolonged encephalopathy lasting up to 173 days was noted
- Serious events including leukoencephalopathy and seizures occurred with YESCARTA®
- Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA®
The following are common signs and symptoms of neurologic toxicities:

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Aphasia</td>
<td>Headache</td>
</tr>
<tr>
<td>Delirium</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Tremor</td>
</tr>
</tbody>
</table>
Guidance on Managing Neurologic Toxicities

- 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 nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities
- Monitor patients at least daily for 7 days at the certified hospitals and their associated clinics following infusion for signs and symptoms of neurologic toxicities
- Monitor patients for signs or symptoms of neurologic toxicities for 4 weeks after infusion and treat promptly
# Guidance on Managing Neurologic Toxicities

## Grading and Management of YESCARTA®-Related Neurologic Toxicities

<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>Supportive care</td>
<td>Supportive care</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>
</tbody>
</table>

| **Grade 2**      | Administer tocilizumab per the table on slide 17 for management of Grade 2 CRS | Continue tocilizumab use until the event is Grade 1 or less, then taper over 3 days |
| Examples include:| If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids | Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis |
| Somnolence—moderate, limiting instrumental ADLs | | |
| Confusion—moderate disorientation | | |
| Encephalopathy—limiting instrumental ADLs | | |
| Dysphasia—moderate, impairing ability to communicate spontaneously | | |
| Seizure(s) | | |

Abbreviation: ADLs, activities of daily living.

# Guidance on Managing Neurologic Toxicities

## Grading and Management of YESCARTA®-Related Neurologic Toxicities

<table>
<thead>
<tr>
<th>Neurologic Event (Grading Assessment CTCAE 4.03)*</th>
<th>Concurrent CRS</th>
<th>No Concurrent CRS</th>
</tr>
</thead>
<tbody>
<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></td>
<td></td>
</tr>
<tr>
<td>Confusion—severe disorientation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Encephalopathy—limiting self-care ADLs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly</td>
<td>Administer tocilizumab per the table on slide 17 for management of Grade 2 CRS</td>
<td>Administer dexamethasone 10 mg intravenous every 6 hours until the event is Grade 1 or less, then taper over 3 days</td>
</tr>
<tr>
<td></td>
<td>In addition, administer dexamethasone 10 mg intravenous with the first dose of tocilizumab and repeat dose every 6 hours</td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
<td></td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening consequences</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent intervention indicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requirement for mechanical ventilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider cerebral edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Administer tocilizumab per the table on slide 17 for management of Grade 2 CRS</td>
<td>Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above</td>
</tr>
<tr>
<td></td>
<td>Administer methylprednisolone 1000 mg intravenous per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenous per day for 2 more days; if improves, then manage as above</td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ADLs, activities of daily living.

Adverse Event Reporting

Reporting suspected adverse events after administration of therapy is important. It allows continued monitoring of the risk/benefit balance of therapy.

Healthcare providers are encouraged to report any suspected serious adverse events associated with YESCARTA® by contacting Kite at 1-844-454-KITE or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Patient Counseling
Patient Counseling

- Talk to the patient about the risk of CRS and neurologic toxicities. Tell them to contact their healthcare provider 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® 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.

- 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® infusion.
YESCARTA® REMS Program Kit

Includes:

• YESCARTA® full Prescribing Information and Medication Guide
• YESCARTA® REMS Program Live Training
• YESCARTA® REMS Program Knowledge Assessment
• YESCARTA® REMS Program Hospital Enrollment Form
• YESCARTA® Adverse Reaction Management Guide
• YESCARTA® Patient Wallet Card
Additional YESCATRA® REMS Program Information and Resources

To enroll in the YESCATRA® REMS Program or obtain information regarding enrollment in the program, call 1-844-454-KITE or visit the YESCATRA® REMS Program website at www.YESCATRAREMS.com. The REMS Program website contains the most current version of REMS-related materials.
What Is the YESCARTA® REMS Program?

A REMS (Risk Evaluation and Mitigation Strategy) 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® outweigh the risks of cytokine release and neurologic toxicities. YESCARTA® is available only through the YESCARTA® REMS Program.

Boxed Warning

Cytokine Release Syndrome

- Cytokine release syndrome (CRS), including fatal or life-threatening reactions, occurred following treatment with YESCARTA®
- CRS occurred in 94% (101/108) of patients receiving YESCARTA® including Grade 3 or higher CRS in 13% (114/108) of patients
- Among patients who died after receiving YESCARTA®, 4 had ongoing CRS events at the time of death
- The median time to onset was 2 days (range: 1-12 days), and the median duration of CRS was 7 days (range: 2-58 days)
- Key manifestations of CRS include fever (78%), hypotension (41%), tachycardia (28%), hypoxia (22%), and chills (20%)
- Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
Neurologic Toxicities

- Neurologic toxicities that were fatal or life-threatening, occurred following treatment with YESCARTA®
- The median time to onset was 4 days (range: 1-43 days) following YESCARTA® infusion
- Neurologic toxicities occurred in 87% of patients with a median duration of 17 days
- 98% of all neurologic toxicities occurred within the first 8 weeks of YESCARTA® infusion
- Grade 3 or higher neurologic toxicities occurred in 31% of patients
- The most common neurologic toxicities included encephalopathy (157%), headache (44%), tremor (31%), dizziness (21%), aphasia (18%), delirium (17%), insomnia (9%), and anxiety (9%)
- Prolonged encephalopathy lasting up to 173 days was noted
- Serious events including leukoencephalopathy and seizures occurred with YESCARTA®
- Fatal and serious cases of cerebral edema have occurred in patients treated with YESCARTA®

YESCARTA® REMS Program Requirements

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

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

Hospital Enrollment Instructions

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

1. Complete the training program, which includes review of:
   - YESCARTA® full Prescribing Information
   - YESCARTA® REMS Program Live Training
   - YESCARTA® Adverse Reaction Management Guide
2. Successfully complete the YESCARTA® REMS Program Knowledge Assessment.
3. Complete the YESCARTA® REMS Program Hospital Enrollment Form.
4. Oversee implementation and compliance with YESCARTA® REMS Program requirements:

- Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA® are trained on the REMS Program requirements and successfully complete the YESCARTA® 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® infusion.
- Put processes and procedures in place to ensure that relevant new staff are trained and relevant staff are retrained if YESCARTA® has not been dispensed at least once annually from the date of certification in the YESCARTA® REMS Program.

**Indication**

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

**Where to Find YESCARTA® REMS Program Information and Resources**

For more information about the YESCARTA® REMS Program, see the Program Resources or call 1-844-454-KITE.
Reporting Adverse Reactions

You are encouraged to report suspected serious adverse events associated with YESCARTA® by contacting Kite at 1-844-454-KITE (1-844-454-5483) or the FDA at www.fda.gov/medwatch or 1-800-FDA-1088.
YEscarTa® Patient Wallet Card

All patients treated with YESCARTA® receive a Patient Wallet Card listing adverse reactions and other information. Patients should show the card 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.

Arabic          Korean

Chinese         Polish

English         Portuguese

French          Russian

German          Spanish

Japanese
Need Help?
If you have questions about the YESCARTA® REMS Program or need help registering, call 1-844-454-KITE, Monday through Friday.

LEFT HAND CORNER:
Resources for Healthcare Professionals
Download All Resources
YESCARTA® Prescribing Information and Medication Guide
YESCARTA® REMS Program Knowledge Assessment
YESCARTA® REMS Program Live Training
YESCARTA® REMS Program Registration Hospital Enrollment Form
YESCARTA® Adverse Reaction Management Guide
Patient Resources
YESCARTA® Patient Wallet Card
YESCARTA® Prescribing Information and Medication Guide
Adobe Reader is required to view PDFs. If you do not have it installed, download it here.
YE.SCARTA® REMS Program Hospital Enrollment Form

YE.SCARTA® REMS Program Hospital Enrollment

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

YE.SCARTA® 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 YE.SCARTA® REMS Program Live Training, complete the YE.SCARTA® REMS Program Knowledge Assessment, complete a new YE.SCARTA® REMS Program Hospital Enrollment Form, and submit the forms via fax to 1-310-496-0397 or email at YE.SCARTAREMS@kitepharma.com.
- Report any serious adverse events suggestive of CRS or neurologic toxicities.
- Report suspected serious adverse events associated with YE.SCARTA® by contacting Kite at 1-844-454-KITE or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
- Dispense YE.SCARTA® 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).
- Maintain documentation of all processes and procedures for the YE.SCARTA® 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.

YE.SCARTA® REMS Program Hospital Registration Form

Please email the completed form to YE.SCARTAREMS@kitepharma.com or fax to 1-310-496-0397.

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 YE.SCARTA®. Please contact 1-844-454-KITE or visit the YE.SCARTA® REMS Program website at www.YESCARTAREMS.com for more information.

YE.SCARTA® REMS Program Hospital Enrollment Form

To finalize your registration in the YE.SCARTA® REMS Program, please complete the form below in its entirety.

- [ ] New Certification
- [ ] Recertification

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® Authorized Representative Attestations

I am the authorized representative designated by my hospital and its associated clinics to coordinate the activities of the YESCARTA® 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® REMS Program Live Training and successfully complete the YESCARTA® REMS Program Knowledge Assessment.

• I must submit this completed YESCARTA® REMS Program Hospital Enrollment Form to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com.

• I must submit the YESCARTA® REMS Program Knowledge Assessment to Kite via fax at 1-310-496-0397 or email to YESCARTAREMS@kitepharma.com.

• I will oversee implementation and compliance with the YESCARTA® REMS Program.

• I will ensure that my 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® REMS Program, including the following, before administering YESCARTA®:
  
• Ensure that all relevant staff involved in the prescribing, dispensing, or administering of YESCARTA® are trained on the REMS Program requirements as described in the training materials, successfully complete the YESCARTA® REMS Program Knowledge Assessment, and maintain training records for all staff.

• Put processes and procedures in place to ensure that relevant staff involved in the prescribing, dispensing, or administering of YESCARTA® are retrained if YESCARTA® has not been dispensed at least once annually from the date of certification in the YESCARTA® REMS Program.

• Prior to dispensing YESCARTA®, 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).

• 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® infusion.

Authorized Representative Name

Title

Signature

Date