

# **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: 07/2020

### **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:**

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

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|---------------------------------|--|
| To become certified to dispense | <ol style="list-style-type: none"><li>1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).</li><li>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.</li><li>3. Have the authorized representative enroll in the REMS by completing the <a href="#">Hospital Enrollment Form</a> and submitting it to the REMS Program.</li><li>4. Have the authorized representative complete the <a href="#">Program Training</a>.</li><li>5. Have the authorized representative successfully complete a <a href="#">Knowledge Assessment</a> and submit it to the REMS Program.</li><li>6. Train all relevant staff involved in prescribing, dispensing, or administering of YESCARTA and/or TECARTUS on the REMS Program requirements using the <a href="#">Program Training</a> and <a href="#">Adverse Reaction Management Guide</a>.</li><li>7. Have all relevant staff involved in prescribing, dispensing, or administering YESCARTA and/or TECARTUS successfully complete the <a href="#">Knowledge Assessment</a>.</li><li>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 <a href="#">Knowledge Assessment</a>.</li><li>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).</li><li>10. Establish processes and procedures to provide patients with the <a href="#">Patient Wallet Card</a>.</li></ol> <hr/> |
| Before infusion                 | <ol style="list-style-type: none"><li>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.</li></ol> <hr/>  |

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

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Before discharge                      12. Provide the patient with the [Patient Wallet Card](#) through the processes and procedures established as a requirement of the REMS Program.

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To maintain certification to dispense, if there is a change in authorized representative                      13. Have the new authorized representative enroll in the REMS Program by completing the [Hospital Enrollment Form](#).

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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](#).

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At all times                      16. Report any serious adverse events<sup>1</sup> 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.

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

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

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<sup>1</sup> 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](http://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 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 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](#)

## 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)
- 呼吸困难
- 发冷或寒战
- 意识模糊
- 眩晕或头晕
- 重度恶心、呕吐或腹泻
- 心跳加快或不规则
- 重度疲乏或虚弱

YESCARTA、YESCARTA 徽标、TECARTUS、TECARTUS 徽标、KITE 和 KITE 徽标是 Kite Pharma, Inc. 的商标。GILEAD 是 Gilead Sciences, Inc. 的商标。  
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折叠



## 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](http://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

YESCARTA, the YESCARTA Logo, TECARTUS, the TECARTUS Logo, KITE, and the KITE Logo are trademarks of Kite Pharma, Inc. GILEAD is a trademark of Gilead Sciences, Inc.

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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](http://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)
- Mareos o aturdimiento
- Dificultad para respirar
- Náuseas, vómitos o diarrea intensos
- Escalofríos o temblores
- Latido cardíaco rápido o irregular
- Confusión
- Fatiga o debilidad intensa

YESCARTA, el logotipo de YESCARTA, TECARTUS, el logotipo de TECARTUS, KITE, y el logotipo de KITE son marcas comerciales de Kite Pharma, Inc. GILEAD es una marca comercial de Gilead Sciences, Inc.

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DOBLAR



## 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

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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.yescartatecartusrem.com](http://www.yescartatecartusrem.com) para obtener más información.

## YESCARTA (axicabtagene ciloleucel) and TECARTUS (brexucabtagene autoleucel) Adverse Reaction Management Guide

This follow-up guidance is supplemental to the YESCARTA<sup>®</sup> US Prescribing Information (USPI).

### 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<sup>®</sup>. This includes the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS.

### CRS Grading and Management Guidance

CRS Grade*	Tocilizumab	Corticosteroids
<b>Grade 1</b> Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	N/A	N/A
<b>Grade 2</b> Symptoms require and respond to moderate intervention  Oxygen requirement less than 40% FiO <sub>2</sub> or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity†	Administer tocilizumab‡ 8 mg/kg intravenous 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
<b>Grade 3</b> Symptoms require and respond to aggressive intervention  Oxygen requirement greater than or equal to 40% FiO <sub>2</sub> 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 (eg, 10 mg intravenous every 6 hours)  Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days
<b>Grade 4</b> 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

Abbreviation: CVVHD, continuous veno-venous hemodialysis.

\*Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

†Refer to page 2 on the back for management of neurologic toxicity.

‡Refer to tocilizumab Prescribing Information for details.

## 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<sup>®</sup>. This includes the use of corticosteroids or corticosteroids and tocilizumab for moderate, severe, or life-threatening neurologic toxicities.

## Neurologic Toxicity Grading and Management Guidance

Neurologic Event (Grading Assessment CTCAE 4.03)*	Concurrent CRS	No Concurrent CRS
<b>Grade 1</b> Examples include: Somnolence—mild drowsiness or sleepiness Confusion—mild disorientation Encephalopathy—mild limiting of ADLs Dysphasia—not impairing ability to communicate	Supportive care	Supportive care
<b>Grade 2</b> Examples include: Somnolence—moderate, limiting instrumental ADLs Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab per the table on the other side for management of Grade 2 CRS If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenous every 6 hours if not already taking other corticosteroids Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	Administer dexamethasone 10 mg intravenous every 6 hours Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
<b>Grade 3</b> 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 the other side for management of Grade 2 CRS 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 Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	Administer dexamethasone 10 mg intravenous every 6 hours Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
<b>Grade 4</b> Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab per the table on the other side for management of Grade 2 CRS 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	Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis

Abbreviation: ADLs, activities of daily living.

\*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

## YESCARTA and TECARTUS Adverse Reaction Management Guide

This follow-up guidance is supplemental to the TECARTUS<sup>™</sup> US Prescribing Information (USPI).

### 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 TECARTUS<sup>™</sup>.

### CRS Grading and Management Guidance

CRS Grade*	Tocilizumab	Corticosteroids
<b>Grade 1</b> Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	If not improving after 24 hours, administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)	N/A
<b>Grade 2</b> Symptoms require and respond to moderate intervention  Oxygen requirement less than 40% FiO <sub>2</sub> or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity†	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	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab  If improving, taper corticosteroids, and manage as Grade 1
<b>Grade 3</b> Symptoms require and respond to aggressive intervention  Oxygen requirement greater than or equal to 40% FiO <sub>2</sub> or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	Per Grade 2  If improving, discontinue tocilizumab	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  If improving, manage as Grade 2  If not improving, manage as Grade 4
<b>Grade 4</b> Life-threatening symptoms  Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)	Per Grade 2  If improving, discontinue tocilizumab	Administer methylprednisolone 1000 mg intravenously per day for 3 days  If improving, taper corticosteroids, and manage as Grade 3  If not improving, consider alternate immunosuppressants

Abbreviation: CVVHD, continuous veno-venous hemodialysis.

\*Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

†Refer to page 4 on the back for management of neurologic toxicity.

‡Refer to tocilizumab Prescribing Information for details.

## 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 TECARTUS™.

### Neurologic Toxicity Grading and Management Guidance

Neurologic Event*	Concurrent CRS	No Concurrent CRS
<b>Grade 1</b> Examples include: Somnolence—mild drowsiness or sleepiness Confusion—mild disorientation Encephalopathy—mild limiting of ADLs Dysphasia—not impairing ability to communicate	Administer tocilizumab per the table on the other side for management of Grade 1 CRS	Supportive care
<b>Grade 2</b> Examples include: Somnolence—moderate, limiting instrumental ADLs Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab per the table on the other side for management of Grade 2 CRS  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  If improving, discontinue tocilizumab  If still not improving, manage as Grade 3	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less  If improving, taper corticosteroids
	Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	
<b>Grade 3</b> 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 the other side for management of Grade 2 CRS  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  If improving, discontinue tocilizumab and manage as Grade 2  If still not improving, manage as Grade 4	Administer dexamethasone 10 mg intravenously every 6 hours  Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids  If not improving, manage as Grade 4
	Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	
<b>Grade 4</b> Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab per the table on the other side for management of Grade 2 CRS  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  If not improving, consider alternate immunosuppressants	Administer methylprednisolone 1000 mg intravenously per day for 3 days  If improving, then manage as Grade 3  If not improving, consider alternate immunosuppressants
	Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	

Abbreviation: ADLs, activities of daily living.

\*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*.



# 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 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 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 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.

- New Certification     Recertification     Change in Authorized Representative

**Authorized Representative Information:**

First Name: \_\_\_\_\_ Last Name: \_\_\_\_\_

Title: \_\_\_\_\_ Credentials:    DO    MD    RPh    RN/NP    PA    Other: \_\_\_\_\_

Phone Number: \_\_\_\_\_ Fax Number: \_\_\_\_\_

Email Address: \_\_\_\_\_

(Continued on next page)

**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 or email to YTREMS@kitepharma.com.
  - I must submit the YESCARTA and TECARTUS REMS Program Knowledge Assessment training online on the REMS Program 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:
    - 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.
    - 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.
    - 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).
    - 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



## 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.

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](mailto:YTREMS@kitepharma.com) or faxed to **1-310-496-0397**.

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

### Questions

1. Prior to discharge, a YESCARTA and TECARTUS REMS Patient Wallet Card must be given to 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 following YESCARTA infusion? It typically occurs:
  - A. With a median time to onset of 7 days for patients with LBCL and 10 days for patients with iNHL
  - B. With a median time to onset of 5 days for patients with LBCL and 6 days for patients with iNHL
  - C. With a median time to onset of 2 days for patients with LBCL and 4 days for patients with iNHL
  - D. Rarely starts during the first week
5. Which of the following is true regarding the time to onset of CRS following TECARTUS infusion? It typically occurs:
  - A. With a median time to onset of 3 days
  - B. With a median time to onset of 5 days
  - C. With a median time to onset of 10 days
  - D. Rarely starts during the first week

*(Continued on next page)*

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 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 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. Appropriate management for this patient would include (please select single best answer):
- A. Consider non-sedating, anti-seizure medicines (eg, 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 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% FiO<sub>2</sub>, 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 \_\_\_\_\_

Hospital/Associated Clinic Name \_\_\_\_\_

Address \_\_\_\_\_

City \_\_\_\_\_ State \_\_\_\_\_ ZIP Code \_\_\_\_\_

Signature \_\_\_\_\_ Date \_\_\_\_\_



## Risk Evaluation and Mitigation Strategy (REMS) Program Training

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.

## Indication — YESCARTA®

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.

- 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.

## Indication — TECARTUS®

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.

Please see full Prescribing Information, including **BOXED WARNING** and Medication Guide.

# YESCARTA and TECARTUS REMS Program Overview

# What is the YESCARTA and TECARTUS 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 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.

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

- 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
- Ensuring that those relevant individuals who prescribe, dispense, or administer YESCARTA and/or TECARTUS are aware of how to manage the risks of CRS and neurologic toxicities

# Hospital Certification

To become certified to dispense YESCARTA and/or TECARTUS, hospitals and their associated clinics must:

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
2. Ensure that the authorized representative oversees implementation and compliance with the YESCARTA and TECARTUS REMS Program requirements
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
4. Recertify in the YESCARTA and TECARTUS REMS Program if a new authorized representative is designated

*(continued on next page)*

## Hospital Certification (continued)

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
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
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 and TECARTUS REMS Program Hospital Enrollment Form.

# 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 or email to YTREMS@kitepharma.com
- Submit the YESCARTA and TECARTUS REMS Program Knowledge Assessment 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

*(continued on next page)*

# YESCARTA and TECARTUS REMS 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 YESCARTA and TECARTUS REMS Program, including the following, before administering YESCARTA and/or TECARTUS:
  - 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
  - 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
  - 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)
  - Prior to patient discharge, provide patients/caregivers with the Patient Wallet Card

# Serious Risks of YESCARTA and TECARTUS



# 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

# 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

# Management of CRS

## Cytokine Release Syndrome — YESCARTA

- CRS, including fatal or life-threatening reactions, occurred following treatment with YESCARTA
- CRS occurred in 94% (101/108) of patients with LBCL in ZUMA-1, including  $\geq$  Grade 3 CRS in 13%
- CRS occurred in 84% (123/146) of patients with indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5, including  $\geq$  Grade 3 CRS in 8% (11/146) of patients with iNHL
- The median time to onset of CRS was 2 days (range, 1-12 days) for patients with LBCL and 4 days (range, 1-20 days) for patients with iNHL
- The median duration of CRS was 7 days (range, 2-58 days) for patients with LBCL and 6 days (range, 1-27 days) for patients with iNHL
- 45% (49/108) of patients with LBCL 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 LBCL patients and 1 iNHL patient had ongoing CRS events at the time of death

## Cytokine Release Syndrome — TECARTUS

- CRS, including life-threatening reactions, occurred following treatment with TECARTUS
- In a Kite clinical trial, CRS occurred in 91% (75/82) of patients receiving TECARTUS, including Grade 3 or higher CRS in 18% of patients
- Among the patients who died after receiving TECARTUS, one had a fatal CRS event
- The median time to onset was 3 days (range, 1-13 days)
- The median duration of CRS was 10 days (range, 1-50 days)

# Patient Assessment of CRS Associated with YESCARTA

The following are signs and symptoms of CRS in all patients combined	
Capillary leak syndrome	Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS)
Cardiac arrest	Hypotension
Cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia)	Hypoxia
Cardiac failure	Multi-organ failure
Chills	Renal insufficiency
Fever	Tachycardia
Headache	

# Patient Assessment of CRS Associated with **TECARTUS**

The following are signs and symptoms of CRS with TECARTUS	
Alanine aminotransferase increase	Fever
Aspartate aminotransferase increased	Headache
Acute kidney injury	Hypotension
Chills	Hypoxia
Diarrhea	Nausea
Fatigue	Tachycardia

# Guidance on Managing CRS for YESCARTA

- 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 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

# Guidance on Management of CRS for YESCARTA

## Grading and Management of YESCARTA-Related CRS

CRS Grade*	Tocilizumab	Corticosteroids
<b>Grade 1</b> Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	N/A	N/A
<b>Grade 2</b> Symptoms require and respond to moderate intervention Oxygen requirement less than 40% FiO <sub>2</sub> or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity†	Administer tocilizumab‡ 8 mg/kg intravenous 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
<b>Grade 3</b> Symptoms require and respond to aggressive intervention Oxygen requirement greater than or equal to 40% FiO <sub>2</sub> 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 (eg, 10 mg intravenous every 6 hours) Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days
<b>Grade 4</b> 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

Abbreviation: CVVHD, continuous veno-venous hemodialysis.

\*Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

†Refer to the table on slide 30 for management of neurologic toxicity.

‡Refer to tocilizumab Prescribing Information for details.

# 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
- Tocilizumab, an interleukin-6 receptor antagonist, is recommended for the management of Grade 1 or higher CRS associated with TECARTUS
- 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 for TECARTUS

## Grading and Management of TECARTUS-Related CRS

CRS Grade*	Tocilizumab	Corticosteroids
<b>Grade 1</b> Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	If not improving after 24 hours, administer tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg)	N/A
<b>Grade 2</b> Symptoms require and respond to moderate intervention Oxygen requirement less than 40% FiO <sub>2</sub> or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity†	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	Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab If improving, taper corticosteroids, and manage as Grade 1
<b>Grade 3</b> Symptoms require and respond to aggressive intervention Oxygen requirement greater than or equal to 40% FiO <sub>2</sub> or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis	Per Grade 2 If improving, discontinue tocilizumab	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (eg, 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids If improving, manage as Grade 2 If not improving, manage as Grade 4
<b>Grade 4</b> Life-threatening symptoms Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)	Per Grade 2 If improving, discontinue tocilizumab	Administer methylprednisolone 1000 mg intravenously per day for 3 days If improving, taper corticosteroids, and manage as Grade 3 If not improving, consider alternate immunosuppressants

Abbreviation: CVVHD, continuous veno-venous hemodialysis.

\*Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124(2):188-195.

†Refer to the table on slide 32 for management of neurologic toxicity.

‡Refer to tocilizumab Prescribing Information for details.

# Management of Neurologic Toxicities

## Neurologic Toxicities — YESCARTA

- Neurologic toxicities that were fatal or life-threatening occurred following treatment with YESCARTA
- Neurologic toxicities occurred in 87% (94/108) of patients with LBCL, including  $\geq$  Grade 3 in 31%
- Neurologic toxicities occurred in 77% (112/146) of patients with iNHL, including  $\geq$  Grade 3 in 21%
- Neurologic toxicities occurred within the first 7 days of YESCARTA infusion for 89% of affected patients with LBCL and 74% of affected patients with iNHL
- The median time to onset was 4 days (range, 1-43 days) for patients with LBCL and 6 days (range, 1-79 days) for patients with iNHL
- The median duration was 17 days in patients with LBCL and 16 days in patients with iNHL
- 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

## Neurologic Toxicities — TECARTUS

- Neurologic events, including those that were life-threatening, occurred following treatment with TECARTUS
- Neurologic events occurred in 81% of patients, 37% of whom experienced Grade 3 or higher (severe or life threatening) adverse reactions
- 85% of all treated patients experienced the first CRS or neurological event within the first 7 days after TECARTUS infusion
- The median time to onset was 6 days (range, 1-32 days) following TECARTUS infusion
- The median duration was 21 days (range, 2-454 days)
- Serious events including encephalopathy, aphasia, and seizures occurred with TECARTUS

# Patient Assessment of Neurologic Toxicities Associated With YESCARTA

The following are common signs and symptoms of neurologic toxicities in all patients combined	
Aphasia	Headache
Delirium	Insomnia
Dizziness	Tremor
Encephalopathy	

# Patient Assessment of Neurologic Toxicities Associated With TECARTUS

The following are common signs and symptoms of neurologic toxicities	
Aphasia	Headache
Delirium	Tremor
Encephalopathy	

# 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
- Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities
- Consider non-sedating, anti-seizure 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 for YESCARTA

## Grading and Management of YESCARTA-Related Neurologic Toxicities

Neurologic Event (Grading Assessment CTCAE 4.03)*	Concurrent CRS	No Concurrent CRS
<b>Grade 1</b> Examples include: Somnolence—mild drowsiness or sleepiness Confusion—mild disorientation Encephalopathy—mild limiting of ADLs Dysphasia—not impairing ability to communicate	Supportive care	Supportive care
<b>Grade 2</b> Examples include: Somnolence—moderate, limiting instrumental ADLs Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab per the table on slide 21 for management of Grade 2 CRS If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenous every 6 hours if not already taking other corticosteroids Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	Administer dexamethasone 10 mg intravenous every 6 hours Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider nonsedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis

Abbreviation: ADL=activities of daily living.

\*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

# Guidance on Managing Neurologic Toxicities for YESCARTA

## Grading and Management of YESCARTA-Related Neurologic Toxicities (continued)

Neurologic Event (Grading Assessment CTCAE 4.03)*	Concurrent CRS	No Concurrent CRS
<p><b>Grade 3</b> 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</p>	<p>Administer tocilizumab per the table on slide 21 for management of Grade 2 CRS 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 Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</p>	<p>Administer dexamethasone 10 mg intravenous every 6 hours Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</p>
<p><b>Grade 4</b> Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema</p>	<p>Administer tocilizumab per the table on slide 21 for management of Grade 2 CRS 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 non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</p>	<p>Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis</p>

Abbreviation: ADL=activities of daily living.

\*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*. Version 4.03. Bethesda, MD: National Institutes of Health; 2009. Revised June 2010. NIH publication 09-5410.

# Guidance on Managing Neurologic Toxicities for TECARTUS

## Grading and Management of TECARTUS-Related Neurologic Toxicities

Neurologic Event*	Concurrent CRS	No Concurrent CRS
<b>Grade 1</b> Examples include: Somnolence—mild drowsiness or sleepiness Confusion—mild disorientation Encephalopathy—mild limiting of ADLs Dysphasia—not impairing ability to communicate	Administer tocilizumab per the table on slide 23 for management of Grade 1 CRS	Supportive care
<b>Grade 2</b> Examples include: Somnolence—moderate, limiting instrumental ADLs Confusion—moderate disorientation Encephalopathy—limiting instrumental ADLs Dysphasia—moderate impairing ability to communicate spontaneously Seizure(s)	Administer tocilizumab per the table on slide 23 for management of Grade 2 CRS 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 If improving, discontinue tocilizumab If still not improving, manage as Grade 3	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less If improving, taper corticosteroids
	Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	

Abbreviation: ADL=activities of daily living.

\*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*.

# Guidance on Managing Neurologic Toxicities for **TECARTUS**

## Grading and Management of TECARTUS-Related Neurologic Toxicities (continued)

Neurologic Event*	Concurrent CRS	No Concurrent CRS
<b>Grade 3</b> 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 slide 23 for management of Grade 2 CRS 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 If improving, discontinue tocilizumab and manage as Grade 2 If still not improving, manage as Grade 4	Administer dexamethasone 10 mg intravenously every 6 hours Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids If not improving, manage as Grade 4
	Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	
<b>Grade 4</b> Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab per the table on slide 23 for management of Grade 2 CRS 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 If not improving, consider alternate immunosuppressants	Administer methylprednisolone 1000 mg intravenously per day for 3 days If improving, then manage as Grade 3 If not improving, consider alternate immunosuppressants
	Consider non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	

Abbreviation: ADL=activities of daily living.

\*National Institutes of Health, National Cancer Institute. *Common Terminology Criteria for Adverse Events (CTCAE)*.

# Adverse Event Reporting

# Adverse Event Reporting

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

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](mailto:medinfo@kitepharma.com) or FDA at **1-800-FDA-1088** or [www.fda.gov/medwatch](http://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

# 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 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

# YESCARTA and TECARTUS REMS Program Resources

# YESCARTA and TECARTUS REMS Program Kit

Includes:

- YESCARTA full Prescribing Information and Medication Guide
- TECARTUS full Prescribing Information and Medication Guide
- YESCARTA and TECARTUS REMS Program Training
- YESCARTA and TECARTUS REMS Program Knowledge Assessment
- YESCARTA and TECARTUS REMS Program Hospital Enrollment Form
- YESCARTA and TECARTUS Adverse Reaction Management Guide
- YESCARTA and TECARTUS Patient Wallet Card

# 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](http://www.YescartaTecartusREMS.com). The REMS Program website contains the most current version of REMS-related materials.

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