YESCARTA®
(axicabtagene ciloleucel) Suspension for IV infusion

TECARTUS®
(brexucabtagene autoleucel) Suspension for IV infusion

Risk Evaluation and Mitigation Strategy (REMS) Program Training

FOR TRAINING PURPOSES ONLY

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.

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Indication — YESCARTA®

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

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

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

Limitation of Use: YESCARTA is not indicated for the treatment of patients with primary central nervous system lymphoma.

- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

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

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.

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

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

YESCARTA and TECARTUS REMS Program Overview

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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

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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, email to YTREMS@kitepharma.com, or online at www.KiteREMSTraining.com
- ☐ Submit the YESCARTA and TECARTUS REMS Program Knowledge Assessment online on the REMS Program Training website or send to Kite via fax at 1-310-496-0397 or email to YTREMS@kitepharma.com
- ☐ Oversee implementation and compliance with the YESCARTA and TECARTUS REMS Program

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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

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

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 90% (379/422) of patients with non-Hodgkin lymphoma (NHL) receiving YESCARTA, including ≥ Grade 3 CRS in 9%
- CRS occurred in 93% (256/276) of patients with large B-cell lymphoma (LBCL), including ≥ Grade 3 CRS in 9%
- CRS occurred in 84% (123/146) of patients with indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5, including ≥ Grade 3 CRS in 8%
- For patients with LBCL, the median time to onset of CRS in:
    - ZUMA-1 was 2 days following infusion (range: 1-12 days)
    - ZUMA-7 was 3 days following infusion (range: 1-10 days)

  For patients with iNHL, the median time to onset of CRS was 4 days (range: 1-20 days)
- For patients with LBCL, the median duration of CRS in:
    - ZUMA-1 was 7 days (range: 2-58 days)
    - ZUMA-7 was 7 days (range: 2-43 days)

  For patients with iNHL, the median duration of CRS was 6 days (range: 1-27 days)
- 45% (49/108) of patients with LBCL in ZUMA-1, and 67% (112/168) of patients with LBCL in ZUMA-7 received tocilizumab after infusion of YESCARTA
- 51% (75/146) of patients with iNHL received tocilizumab after infusion of YESCARTA
- Among patients who died after receiving YESCARTA, 4 LBCL patients and 1 iNHL patient had ongoing CRS events at the time of death

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Cytokine Release Syndrome — YESCARTA (continued)

- Serious events that may be associated with CRS include, cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), renal insufficiency, cardiac failure, respiratory failure, cardiac arrest, capillary leak syndrome, multi-organ failure and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)
- The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of CRS was assessed in two subsequent cohorts of LBCL patients (ZUMA-1).

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

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

Cytokine Release Syndrome — TECARTUS

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

[1]Lee DW et al (2014). Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014 Jul 10; 124(2): 188-195

Patient Assessment of CRS Associated with YESCARTA[1]

The following are signs and symptoms of CRS in all patients combined	
Chills	Hypotension
Fatigue	Hypoxia
Fever	Tachycardia
Headache	

[1]Reference Section 5.1 (Warning and Precautions/CRS) of the YESCARTA Prescribing Information for a complete list of signs and symptoms for CRS

Patient Assessment of CRS Associated with TECARTUS[1]

The key signs and symptoms of CRS associated with TECARTUS are similar in MCL and ALL and include:	
Chills	Hypotension
Fatigue	Hypoxia
Fever	Nausea
Headache	Tachycardia

[1]Reference Section 5.1 (Warning and Precautions/CRS) of the TECARTUS Prescribing Information for a complete list of signs and symptoms for CRS

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 22
- 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
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If symptoms (e.g., fever) not improving after 24 hours, consider managing as Grade 2.	If not improving after 3 days, administer one dose of dexamethasone 10 mg intravenously.
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low-dose of one vasopressor or Grade 2 organ toxicity.†	Administer tocilizumab‡ 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses. If improving, discontinue tocilizumab.	Administer dexamethasone 10 mg intravenously once daily. If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2. If improving, manage as appropriate grade above.	Dexamethasone 10 mg intravenously three times a day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis (CVVHD), or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2. If improving, manage as appropriate grade above.	Administer methylprednisolone 1000 mg intravenously once per day for 3 days. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider methylprednisolone 1000 mg 2-3 times a day or alternate therapy.†

*Lee et al. 2014.
†Refer to the table on slide 32 for management of neurologic toxicity.
‡Refer to tocilizumab Prescribing Information for details.
†Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

Guidance on Managing 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 24
- 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 daily for at least 7 days for patients with MCL and at least 14 days for patients with ALL at the certified hospitals and their associated clinics following infusion for signs and symptoms of CRS
- 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
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab‡ 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	Not applicable.
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity.†	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.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 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.
Grade 4 Life-threatening symptoms. Requirements for ventilator support, or continuous veno-venous hemodialysis (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.

*Lee et al. 2014.
†Refer to the table on slide 34 for management of neurologic toxicity.
‡Refer to tocilizumab Prescribing Information for details.

Management of Neurologic Toxicities

Neurologic Toxicities — YESCARTA

- Neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome (ICANS)) that were fatal or life-threatening occurred following treatment with YESCARTA
- Neurologic toxicities occurred in 78% (330/422) of patients with NHL receiving YESCARTA, including ≥ Grade 3 cases in 25%
- Neurologic toxicities occurred in 87% (94/108) of patients with LBCL in ZUMA-1, including ≥ Grade 3 cases in 31% and in 74% (124/168) of patients in ZUMA-7 including ≥ Grade 3 cases in 25%
- Neurologic toxicities occurred in 77% (112/146) of patients with iNHL, including ≥ Grade 3 in 21%
- Neurologic toxicities occurred within the first 7 days of YESCARTA infusion for 87% of affected patients with LBCL and 74% of affected patients with iNHL
- For patients with LBCL, the median time to onset of neurologic toxicities in:
    - ZUMA-1 was 4 days (range: 1-43 days)
    - ZUMA-7 was 5 days (range: 1-133 days)

  For patients with iNHL, the median time to onset of neurologic toxicities was 6 days (range: 1-79 days)
- For patients with LBCL, the median duration of neurologic toxicities in:
    - ZUMA-1 was 17 days
    - ZUMA-7 was 15 days

  For patients with iNHL, the median duration was 16 days
- Prolonged encephalopathy lasting up to 173 days was noted

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Neurologic Toxicities — YESCARTA (continued)

- Serious events including aphasia, leukoencephalopathy, dysarthria, lethargy, and seizures occurred in patients treated with YESCARTA
- Fatal and serious cases of cerebral edema and encephalopathy, including late-onset encephalopathy, have occurred in patients treated with YESCARTA
- The impact of earlier treatment with tocilizumab and/or corticosteroids on the incidence and severity of neurologic toxicities was assessed in two subsequent cohorts of LBCL patients (ZUMA-1)

  Among patients who received corticosteroids at the onset of Grade 1 toxicities
  - Neurologic toxicities occurred in 78% (32/41) and 20% (8/41) had Grade 3 neurologic toxicities; no patients experienced a Grade 4 or 5 event
  - The median time to onset of neurologic toxicities was 6 days (range, 1-93 days)
  - The median duration was 8 days (range, 1-144 days)

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

Neurologic Toxicities — TECARTUS

- Neurologic events, including those that were fatal or life-threatening, occurred following treatment with TECARTUS
- Neurologic events occurred in 81% (66/82) of patients with MCL including ≥ Grade 3 in 37% of patients
- Neurologic events occurred in 87% (68/78) of patients with ALL, including ≥ Grade 3 in 35% of patients
- Ninety-one percent of all treated patients (MCL/ALL) experienced the first CRS or neurological event within the first 7 days after TECARTUS infusion
- Nine patients (3 patients with MCL and 6 patients with ALL) had ongoing neurologic events at the time of death
- The median time to onset was 6 days (range, 1-32 days) in patients with MCL
- The median duration was 21 days (range, 2-454 days) in patients with MCL
- The median time to onset was 7 days (range, 1-51 days) in patients with ALL
- The median duration was 15 days (range, 1-397 days) in patients with ALL
- Serious events (≥ 2%) including encephalopathy, aphasia, confusional state, and seizures occurred after treatment with TECARTUS

Patient Assessment of Neurologic Toxicities Associated With YESCARTA[1]

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

[1]Reference Section 5.2 (Warning and Precautions/Neurologic Toxicities) of the YESCARTA Prescribing Information for a complete list of signs and symptoms for neurologic toxicities

Patient Assessment of Neurologic Toxicities Associated With TECARTUS[1]

The most common neurologic events associated with TECARTUS are similar in MCL and ALL and include:	
Agitation	Dizziness
Anxiety	Encephalopathy
Aphasia	Headache
Confusional state	Tremor
Delirium	

[1]Reference Section 5.2 (Warning and Precautions/Neurologic Toxicities) of the TECARTUS Prescribing Information for a complete list of signs and symptoms for neurologic toxicities

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 levetiracetam for seizure prophylaxis for any grade of neurologic toxicities for patients treated with YESCARTA
- Consider levetiracetam for seizure prophylaxis for any Grade 2 of neurologic toxicities for patients treated with TECARTUS
- Monitor patients at least daily for 7 days for patients treated with YESCARTA at the certified hospitals and their associated clinics following infusion for signs and symptoms of neurologic toxicities
- Monitor patients at least daily for 7 days for patients treated with TECARTUS for MCL and at least 14 days for patients treated with TECARTUS for ALL at the certified hospitals and their associated clinics following infusion for signs and symptoms of neurologic toxicities
- 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*	Concurrent CRS	No Concurrent CRS
Grade 1 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 22 for management of Grade 1 CRS. In addition, administer one dose of dexamethasone 10 mg intravenously. If not improving after 2 days, repeat dexamethasone 10 mg intravenously.	Administer one dose of dexamethasone 10 mg intravenously. If not improving after 2 days, repeat dexamethasone 10 mg intravenously.
	Consider levetiracetam for seizure prophylaxis.	
Grade 2 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 22 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously four times a day. If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.	Administer dexamethasone 10 mg intravenously four times a day. If improving, continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. If not improving, manage as appropriate grade below.
	Consider levetiracetam for seizure prophylaxis.	

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

Guidance on Managing Neurologic Toxicities for YESCARTA

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

Neurologic Event*	Concurrent CRS	No Concurrent CRS
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Administer tocilizumab per the table on slide 22 for management of Grade 2 CRS. In addition, administer methylprednisolone 1000 mg intravenously once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.	Administer methylprednisolone 1000 mg intravenously once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.
	Consider levetiracetam for seizure prophylaxis.	
Grade 4 Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab per the table on slide 22 for management of Grade 2 CRS. In addition, administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.**	Administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.**
	Consider levetiracetam for seizure prophylaxis.	

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

Guidance on Managing Neurologic Toxicities for TECARTUS

Grading and Management of TECARTUS-Related Neurologic Toxicities

Neurologic Event*	Concurrent CRS	No Concurrent CRS
Grade 1 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 24 for management of Grade 1 CRS.	Supportive care.
Grade 2 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 24 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, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Abbreviation: ADLs, activities of daily living.
*Severity based on Common Terminology Criteria for Adverse Events.

Guidance on Managing Neurologic Toxicities for TECARTUS

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

Neurologic Event*	Concurrent CRS	No Concurrent CRS
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Administer tocilizumab per the table on slide 24 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, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4 Life-threatening consequences Urgent intervention indicated Requirement for mechanical ventilation Consider cerebral edema	Administer tocilizumab per the table on slide 24 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, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Abbreviation: ADLs, activities of daily living.
*Severity based on Common Terminology Criteria for Adverse Events.

Adverse Event Reporting

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion | TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

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** or **www.Gilead.com** or FDA at **1-800-FDA-1088** or **www.fda.gov/medwatch**.

Healthcare providers are also encouraged to report any suspected serious adverse events* associated with YESCARTA or TECARTUS as outlined above.

*Serious adverse events are defined as any adverse experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect

Patient Counseling

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion | TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

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® (axicabtagene ciloleucel) Suspension for IV infusion

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

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**. The REMS Program website contains the most current version of REMS-related materials.