

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

This follow-up guidance is supplemental to the YESCARTA[®] 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[®]. 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
Grade 1 Symptoms require symptomatic treatment only (eg, fever, nausea, fatigue, headache, myalgia, malaise)	N/A	N/A
Grade 2 Symptoms require and respond to moderate intervention Oxygen requirement less than 40% FiO ₂ 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
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	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
Grade 4 Life-threatening symptoms Requirements for ventilator support, CVVHD, or Grade 4 organ toxicity (excluding transaminitis)	Per Grade 2	Administer methylprednisolone 1000 mg intravenous per day for 3 days; if improves, then manage as above

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[®]. 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
Grade 1 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
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 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 non-sedating, 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 non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis
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 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 non-sedating, 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 non-sedating, antiseizure medicines (eg, 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 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 non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis	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

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[™] 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[™].

CRS Grading and Management Guidance

CRS Grade*	Tocilizumab	Corticosteroids
Grade 1 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
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, and manage as Grade 1
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, 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
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 the other side 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 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	
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 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	
Grade 4 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)*.