

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)

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in the table below. Patients who experience Grade 2 or higher CRS (e.g., hypotension not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

CRS Grading and Management Guidance

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 page 2 for management of neurologic toxicity.

[‡]Refer to tocilizumab Prescribing Information for details.

[†]Alternate therapy includes (but is not limited to): anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG.

Guidance on Managing Neurologic Toxicity

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

Neurologic Toxicity/ICANS Grading and Management Guidance

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 page 1 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 page 1 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.	
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Administer tocilizumab per the table on page 1 for management of Grade 2 CRS. In addition, administer methylprednisolone 1000 mg intravenously once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.	Administer methylprednisolone 1000 mg intravenously once daily. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, manage as Grade 4.
	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 page 1 for management of Grade 2 CRS. In addition, administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.**	Administer methylprednisolone 1000 mg intravenously twice per day. If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. If not improving, consider 1000 mg of methylprednisolone intravenously 3 times a day or alternate therapy.**
	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.

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)

Identify CRS based on clinical presentation. Evaluate for and treat other causes of fever, hypoxia, and hypotension. If CRS is suspected, manage according to the recommendations in the table below. Patients who experience Grade 2 or higher CRS (e.g., hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

CRS Grading and Management Guidance

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 page 4 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. Rule out other causes of neurologic symptoms. Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis for any Grade 2 or higher neurologic toxicities.

Neurologic Toxicity Grading and Management Guidance

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 page 3 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 page 3 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.	
Grade 3 Examples include: Somnolence—obtundation or stupor Confusion—severe disorientation Encephalopathy—limiting self-care ADLs Dysphasia—severe receptive or expressive characteristics, impairing ability to read, write, or communicate intelligibly	Administer tocilizumab per the table on page 3 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 page 3 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.