



BREYANZI® REMS Training

This educational module contains information regarding selected BREYANZI-associated adverse reactions of cytokine release syndrome (CRS) and neurologic toxicities. These are not all of the adverse reactions associated with BREYANZI. Please refer to the BREYANZI Prescribing Information and Medication Guide for more information.

Indication

BREYANZI is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma, after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B.

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

Please see full Prescribing Information including Boxed WARNINGS and Medication Guide.

BREYANZI REMS Overview

About BREYANZI REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program 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. BREYANZI is only available under a restricted program called BREYANZI REMS because of the serious risks of CRS and neurologic toxicities.

The goals of the BREYANZI REMS are to mitigate the risks of CRS and neurologic toxicities by:

- Ensuring that hospitals and associated clinics that dispense BREYANZI are specially certified and have on-site, immediate access to tocilizumab.
- Ensuring that those who prescribe, dispense, or administer BREYANZI are aware of how to manage the risks of CRS and neurologic toxicities.

Certification of Hospitals and Associated Clinics

To become certified to dispense BREYANZI, hospitals and associated clinics must:

1. Designate an authorized representative (AR) to carry out the certification process by completing and submitting the BREYANZI REMS Hospital Enrollment Form on behalf of the hospital and its associated clinics.
2. Ensure the AR oversees implementation and compliance with BREYANZI REMS requirements.
3. Dispense BREYANZI only after verifying that a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for immediate administration (within 2 hours).
4. Ensure that if the hospital or its associated clinics designate a replacement AR, the replacement AR must take the BREYANZI REMS Live Training Program (in-person or via live webcast), complete the BREYANZI REMS Knowledge Assessment, and complete and submit a new BREYANZI REMS Hospital Enrollment Form.

Certification of Hospitals and Associated Clinics (cont'd)

5. Maintain documentation of all processes and procedures for BREYANZI REMS and provide documentation upon request to Juno or to a third party acting on behalf of Juno. Juno Therapeutics, Inc. is a Bristol-Myers Squibb Company.
6. Provide documentation of all processes and procedures for the REMS, requested by Juno, FDA, or a third party acting on behalf of Juno or FDA.
7. Comply with audits by Juno or a third party acting on behalf of Juno to ensure that all training, processes, and procedures are in place and are being followed for BREYANZI REMS.
8. Report any serious* adverse events suggestive of CRS or neurologic toxicities to the REMS program.

*For the purpose of this REMS Program, 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.

Identifying an authorized representative

The AR responsible for the hospital and any associated clinics must have capacity to oversee implementation of, and compliance with, BREYANZI REMS by:

1. Ensuring that all relevant staff are trained, complete the BREYANZI REMS Knowledge Assessment, and maintain records.
2. Having the ability to ensure that processes and procedures related to BREYANZI REMS have been established and are being followed.
3. Having the ability to comply with audits carried out by Juno.

It is not required that the AR be a healthcare provider.

Responsibilities of the BREYANZI REMS authorized representative

To successfully complete BREYANZI REMS certification, the designated AR must:

- Complete the BREYANZI REMS Live Training Program (live in-person or via webcast).
- Submit a successfully completed BREYANZI REMS Knowledge Assessment to Juno online at BreyanziREMS.com, via email REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
- Submit a successfully completed BREYANZI REMS Hospital Enrollment Form to Juno online at BreyanziREMS.com, via email REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
- Oversee the implementation of and compliance with BREYANZI REMS in hospitals and associated clinics.

Responsibilities of the BREYANZI REMS authorized representative (cont'd)

Before administering BREYANZI, establish processes and procedures that are subject to monitoring by Juno or a third party acting on behalf of Juno to help ensure the following:

- All relevant staff involved in prescribing, dispensing, or administering of BREYANZI are trained on the REMS requirements and successfully complete the BREYANZI REMS Knowledge Assessment, and maintain records of staff training (including a retraining process if BREYANZI has not been dispensed at least once annually from the date of initial REMS certification).
- Prior to infusing BREYANZI, verify that 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 infusing BREYANZI, provide patients with the Patient Wallet Card.

Completion of the BREYANZI REMS Training and Knowledge Assessment

The following individuals are recommended to complete BREYANZI REMS Training and the Knowledge Assessment:

- Individuals involved in prescribing, dispensing, and/or administering of BREYANZI.
- Individuals who will be the AR or may complete tasks on behalf of the AR.
- Individuals who may discuss BREYANZI REMS education with patients or provide a REMS wallet card to a patient.
- Individuals involved in the verification, dispensing, and administration of tocilizumab.
- Individuals who may be responsible for reporting adverse events per the REMS program to FDA or the manufacturer.

Note: Juno recognizes that the assignment of REMS activities may be made to different personnel in each healthcare facility. Each healthcare facility should independently assess their REMS training needs to ensure that appropriate personnel are trained.



Serious Risks of Cytokine Release Syndrome and Neurologic Toxicities Associated with Breyanzi

Serious Risks Associated with BREYANZI

WARNING: CYTOKINE RELEASE SYNDROME and NEUROLOGIC TOXICITIES

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving BREYANZI. Do not administer BREYANZI to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab with or without corticosteroids.
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving BREYANZI, including concurrently with CRS, after CRS resolution, or in the absence of CRS. Monitor for neurologic events after treatment with BREYANZI. Provide supportive care and/or corticosteroids as needed.
- BREYANZI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the BREYANZI REMS.

Management of Cytokine Release Syndrome

Cytokine Release Syndrome

- CRS, including fatal or life-threatening reactions, occurred following treatment with BREYANZI.
- CRS occurred in 46% (122/268) of patients receiving BREYANZI, including \geq Grade 3 (Lee grading system¹) CRS in 4% (11/268) of patients.
- The median time to onset was 5 days (range: 1 to 15 days).
- The median duration of CRS was 5 days (range: 1 to 30 days).
- Sixty-one out of 268 (23%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of BREYANZI. Twenty-seven (10%) patients received tocilizumab only, 25 (9%) received tocilizumab and a corticosteroid, and 9 (3%) received corticosteroids only.
- One patient had fatal CRS and 2 had ongoing CRS at time of death.

Signs and Symptoms of CRS

- CRS is a non-antigen specific toxicity that occurs as a result of high-level immune activation.¹
- Clinical symptoms and severity of CRS are highly variable, ranging from mild flu-like symptoms to multiorgan failure. Fever is a hallmark of CRS.
- Management can be complicated by concurrent conditions.

The Most Common Manifestations of CRS Observed in BREYANZI Clinical Trials	
Fever	93%
Hypotension	49%
Tachycardia	39%
Chills	28%
Hypoxia	21%

Managing CRS

- Identify CRS based on clinical presentation.
- Evaluate for and treat other causes of fever, hypoxia, and hypotension.
- Monitor patients daily at a certified healthcare facility during the first week, following infusion for signs and symptoms of CRS and neurologic toxicities.
- Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion.
- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.
- Instruct patients to remain within 2 hours of the certified healthcare facility for at least 4 weeks following infusion.
- If CRS is suspected, manage according to the recommendations on slides 19-20.
- If concurrent neurologic toxicity is suspected during CRS, administer:
 - Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades in slides 19-20 and slides 25-26 respectively. Tocilizumab according to the CRS grade on slides 19-20.
 - Antiseizure medication according to the neurologic toxicity on slides 25-26.

Lee Criteria¹ for CRS Grading

- CRS grading is based on Lee Criteria, shown in table below.
- Final grading should be done after reviewing all of the reported symptoms associated with CRS.

	Symptoms/Signs	CRS Grade 1 (mild)	CRS Grade 2 (moderate)	CRS Grade 3 (severe)	CRS Grade 4 (life-threatening)
			CRS grade is defined by the <u>most severe of the symptoms listed below</u> , excluding fever (ie SBP oxygen requirement and organ toxicity)		
Vital signs					
	Fever	Yes	Any	Any	Any
	Systolic blood pressure (SBP) ≤90 mmHg	N/A	Responds to IV fluids or single low-dose vasopressor	Needs high-dose or multiple vasopressors	Life-threatening
	Need for oxygen to reach oxygen saturation (SaO₂) >90%	N/A	Fraction of inspired oxygen (F _I O ₂) <40%	F _I O ₂ ≥40%	Needs ventilator support
Organ toxicity					
		N/A	Grade 2	Grade 3 or transaminats Grade 4	Grade 4 (excluding transaminats)

F_IO₂, fraction of inspired oxygen V intravenous SaO₂, oxygen saturation

1. Lee DW Gardner R Porter DL et al Current concepts in the diagnosis and management of cytokine release syndrome *Blood* 2014 124 188-195

BREYANZI CRS Grading and Management Guidance

CRS Grade*	When to use tocilizumab	When to use corticosteroids†
Grade 1		
Fever	If <72 hours after infusion, consider tocilizumab 8 mg/kg IV over 1 hour (not to exceed 800 mg). If ≥72 hours after infusion, treat symptomatically.	If <72 hours after infusion, consider dexamethasone 10 mg IV every 24 hours. If ≥72 hours after infusion, treat symptomatically.
Grade 2		
Symptoms require and respond to moderate intervention. Oxygen requirement <40% FIO ₂ , or hypotension responsive to fluids or low dose of one vasopressor, or Grade 2 organ toxicity.	Administer tocilizumab 8 mg/kg IV 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 <72 hours after infusion, administer dexamethasone 10 mg IV every 12 to 24 hours. If ≥72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours.
	If no improvement within 24 hours or rapid progression, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours). If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	

IV intravenous FIO₂ fraction of inspired oxygen

* Lee criteria for grading CRS (Lee et al 2014) † If corticosteroids are initiated continue corticosteroids for at least 3 doses or until complete resolution of symptoms and consider corticosteroid taper

BREYANZI CRS Grading and Management Guidance (cont'd)

CRS Grade*	When to use tocilizumab	When to use corticosteroids†
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement $\geq 40\%$ F_{iO_2} , or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminases.	Per Grade 2. If no improvement within 24 hours or rapid progression of CRS, repeat tocilizumab and escalate dose and frequency of dexamethasone (10-20 mg IV every 6 to 12 hours). If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	Administer dexamethasone 10 mg IV every 12 hours.
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous hemofiltration (CVVHD) or Grade 4 organ toxicity (excluding transaminases).	Per Grade 2. If no improvement within 24 hours or rapid progression of CRS, escalate tocilizumab and corticosteroid use. If no improvement or continued rapid progression, maximize dexamethasone, switch to high-dose methylprednisolone 2 mg/kg if needed. After 2 doses of tocilizumab, consider alternative immunosuppressants. Do not exceed 3 doses tocilizumab in 24 hours, or 4 doses in total.	Administer dexamethasone 20 mg IV every 6 hours.

V intravenous F_{iO_2} fraction of inspired oxygen

* Lee criteria for grading CRS (Lee et al 2014) † If corticosteroids are initiated continue corticosteroids for at least 3 doses or until complete resolution of symptoms and consider corticosteroid taper

Management of Neurologic Toxicities

Clinical Presentation of Neurologic Toxicities

- Neurologic toxicities that were fatal or life-threatening occurred following treatment with BREYANZI.
- Neurologic toxicities occurred in 35% (95/268) of patients receiving BREYANZI, including \geq Grade 3 in 12% (31/268) of patients.
- The onset of all neurologic events occurred within the first 8 weeks following BREYANZI infusion.
- The median time to onset of the first event was 8 days (range: 1 to 46 days).
- Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death.
- Neurologic toxicities resolved in 81 of 95 (85%) patients with a median duration of 12 days (range: 1 to 87 days). Three of four patients with ongoing neurologic toxicity at data cutoff had tremor and one subject had encephalopathy.
- The median duration of neurologic toxicities was 15 days (range: 1 to 785 days).
- The most common neurologic toxicities included encephalopathy (24%), tremor (14%), aphasia (9%), delirium (7%), headache (7%), ataxia (6%), and dizziness (6%).
- Serious events including cerebral edema and seizures occurred with BREYANZI.
- Neurologic toxicities, occurred concurrently with CRS, after CRS resolution or in the absence of CRS.

Management of Neurologic Toxicities

- Identify neurologic toxicity based on clinical presentation.
- Rule out other causes of neurologic symptoms.
- If neurologic toxicity is suspected, manage according to the recommendations on slides 25-26.
- If concurrent CRS is suspected during neurologic toxicity, administer:
 - Corticosteroids according to the more aggressive intervention based on the CRS and neurologic toxicity grades on slides 19-20 and 25-26.
 - Tocilizumab according to the CRS grade on slides 19-20.
 - Antiseizure medication according to the neurologic toxicity on slides 25-26.
- Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities.
- Monitor patients daily at a certified healthcare facility during the first week, following infusion for signs and symptoms of CRS and neurologic toxicities.
- Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion; evaluate and treat promptly.
- Counsel patients and their care partner to seek immediate medical attention should signs and symptoms of neurologic toxicity occur at any time.

CTCAE v4.03 Grading of Individual Neurologic Symptoms of Neurologic Toxicities Used to Determine Overall Grade of Neurologic Toxicities

Adverse event term/Neurotoxicity domain ²	Grade 1	Grade 2	Grade 3	Grade 4
Cerebra edema				Life threatening consequences; urgent intervention indicated
Confusion	Mild disorientation	Moderate disorientation; mild instrumental ADL	Severe disorientation; mild self care ADL	Life threatening consequences; urgent intervention indicated
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; mild instrumental ADL	Difficult to arouse	Life threatening consequences
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly	
Encephalopathy	Mild symptoms	Moderate symptoms; mild instrumental ADL	Severe symptoms; mild self care ADL	Life threatening consequences; urgent intervention indicated
Headache	Mild pain	Moderate pain; mild instrumental ADL	Severe pain; mild self care ADL	
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medication intervention	Life threatening; prolonged repetitive seizures
Tremor	Mild symptoms	Moderate symptoms; mild instrumental ADL	Severe symptoms; mild self care ADL	

ADL: activities of daily living; CTCAE: Common Terminology Criteria for Adverse Events

Neurologic Toxicity Grading and Management Guidance

NT Grade*	Corticosteroids and Antiseizure Medication
<p>Grade 1</p>	<p>Start non-sedating, antiseizure medications (eg, levetiracetam) for seizure prophylaxis.</p> <p>If ≥ 72 hours after infusion, observe.</p> <p>If < 72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days.</p>
<p>Grade 2</p>	<p>Start non-sedating, antiseizure medications (eg, levetiracetam) for seizure prophylaxis.</p> <p>Dexamethasone 10 mg IV every 12 hours for 2 to 3 days, or longer for persistent symptoms. Consider taper for a total steroid exposure of > 3 days.</p> <p>If no improvement after 24 hours or worsening of neurologic toxicity, increase the dose and/or frequency of dexamethasone up to a maximum of 20 mg IV every 6 hours.</p> <p>If no improvement after another 24 hours, rapidly progressing symptoms, or life-threatening complications arise, give methylprednisolone (2 mg/kg loading dose, followed by 2 mg/kg divided 4 times a day; taper within 7 days).</p>

IV intravenous NT neurologic toxicity

* NC CTCAE criteria for grading neurologic toxicities version 4.03

Neurologic Toxicity Grading and Management Guidance

NT Grade*	Corticosteroids and Antiseizure Medication
<p>Grade 3</p>	<p>Start non-sedating, antiseizure medications (e.g., levetiracetam) for seizure prophylaxis.</p> <p>Dexamethasone 10 to 20 mg IV every 8 to 12 hours. Corticosteroids are not recommended for isolated Grade 3 headaches.</p> <p>If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2).</p> <p>If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1 to 2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m².</p>
<p>Grade 4</p>	<p>Start non-sedating, antiseizure medications (e.g., levetiracetam) for seizure prophylaxis.</p> <p>Dexamethasone 20 mg IV every 6 hours.</p> <p>If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2).</p> <p>If cerebral edema is suspected, consider hyperventilation and hyperosmolar therapy. Give high-dose methylprednisolone (1 to 2 g, repeat every 24 hours if needed; taper as clinically indicated), and cyclophosphamide 1.5 g/m².</p>

IV intravenous NT neurologic toxicity

* NC CTCAE criteria for grading neurologic toxicities version 4.03

BREYANZI Infusion Delays

Delay the infusion of BREYANZI if the patient has:

- Unresolved serious adverse events from preceding chemotherapies.
- Active uncontrolled infection.
- Active graft-versus-host disease (GVHD).

Reporting Adverse Events

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

- Hospitals and its associated clinics must report any serious* adverse events suggestive of CRS or neurologic toxicities to Juno at www.bms.com or 1-888-805-4555 or FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.

*For the purpose of this REMS Program, 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.

BREYANZI REMS Program Materials

- BREYANZI REMS Live Training Program
- BREYANZI REMS Knowledge Assessment
- BREYANZI REMS Hospital Enrollment Form
- BREYANZI REMS Patient Wallet Card
- BREYANZI REMS Program Website BreyanziREMS.com

Patient Counseling

Patient Counseling

- Talk to the patient about the risks of CRS and neurologic toxicities and advise patients to seek immediate medical care for any of the following:
 - CRS: Fever, chills, hypotension, tachycardia, hypoxia, and fatigue. Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.
 - Neurologic toxicities: Encephalopathy, confusion, decreased consciousness, speech disorders, tremor, and seizures. Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time.
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Prior to infusion, provide the patient with the Patient Wallet Card.
- Advise patients of the need to:
 - Remain within 2 hours of the certified healthcare facility for at least 4 weeks following infusion.
 - Contact Bristol-Myers Squibb at 1-888-805-4555 if they are diagnosed with a secondary malignancy.
 - Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after BREYANZI administration.

References

1. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. *Blood*. 2014;124:188-195.
2. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

To learn more about BREYANZI REMS, please visit
BreyanziREMS.com or call 1-888-423-5436.