

RISK EVALUATION AND MITIGATION STRATEGY (REMS) DOCUMENT

BREYANZI® (LISOCABTAGENE MARALEUCEL) REMS PROGRAM

I. ADMINISTRATIVE INFORMATION

Application Number: BLA 125714

Application Holder: Juno Therapeutics, Inc., a Bristol-Myers Squibb Company

Initial REMS Approval: XX/2020

II. REMS GOALS

The goals of the BREYANZI REMS are to mitigate the risks of cytokine release syndrome (CRS) and neurological toxicities by:

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

III. REMS REQUIREMENTS

Juno Therapeutics, Inc. must ensure that hospitals and their associated clinics, and patients comply with the following requirements:

1. Hospitals and their associated clinics that dispense BREYANZI must:

To become certified to dispense

1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours).
 2. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program requirements on behalf of the hospital and associated clinic(s).
 3. Have the authorized representative complete the [Live Training Program](#) provided by the REMS Program
 4. Have the authorized representative successfully complete the [Knowledge Assessment](#) and submit it to the REMS Program.
 5. Have the authorized representative enroll in the REMS Program by completing the [Hospital Enrollment Form](#) and submitting it to the REMS Program.
 6. Train all relevant staff involved in prescribing, dispensing, or administering of BREYANZI on the REMS Program requirements using the [Live Training Program](#).
 7. Have all relevant staff involved in prescribing, dispensing, or administering of BREYANZI successfully complete the [Knowledge Assessment](#) and submit it to the REMS Program.
 8. Establish processes and procedures to ensure relevant new staff involved in the prescribing, dispensing, or administration
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	<p>of BREYANZI are trained and complete the Knowledge Assessment and submit it to the REMS Program.</p> <p>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).</p> <p>10. Establish processes and procedures to provide patients with the Patient Wallet Card.</p>
Before infusion	<p>11. Provide the patient with the Patient Wallet Card</p> <p>12. 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.</p>
To maintain certification to dispense, if there is a change in authorized representative	<p>13. Have a new Authorized Representative enroll in the REMS Program by completing the Hospital Enrollment Form.</p>
To maintain certification to dispense, if BREYANZI has not been dispensed at least once annually from the date of certification in the REMS Program	<p>14. Train all relevant staff involved in prescribing, dispensing, or administering of BREYANZI on the REMS Program requirements using the Live Training Program.</p> <p>15. Have all relevant staff involved in prescribing, dispensing, or administering of BREYANZI successfully complete the Knowledge Assessment.</p>
At all times	<p>16. Report any serious¹ adverse events suggestive of cytokine release syndrome or neurological toxicities to the REMS Program.</p> <p>17. Maintain records of staff training.</p> <p>18. Maintain records that processes and procedures are in place and are being followed.</p> <p>19. Comply with audits carried out by Juno Therapeutics, Inc., or a third party acting on behalf of Juno Therapeutics, Inc., to ensure that all training, processes, and procedures are in place and are being followed.</p>

2. Patients who are prescribed BREYANZI:

Before infusion	<p>1. Receive the Patient Wallet Card.</p>
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¹ 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.

Juno Therapeutics Inc. must provide training to relevant staff who prescribe, dispense, or administer BREYANZI.

The training includes the following educational materials: [Live Training Program](#) and [Knowledge Assessment](#). The training must be provided in-person or via live webcast.

To support REMS Program operations, Juno Therapeutics, Inc. must:

1. Ensure BREYANZI is distributed only to certified hospitals or their associated clinics.
2. Establish and maintain the [REMS Program website, www.BreyanziREMS.com](#). The REMS Program website must include the option to print the Prescribing Information (PI), Medication Guide, and REMS materials. All 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 website and call center.
4. Establish and maintain a REMS Program Call Center for REMS participants at 1-888-423-5436.
5. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
6. Ensure hospitals and their associated clinics are able to enroll in the REMS Program in person, online, fax and telephone.
7. Notify hospitals and their associated clinics within 7 calendar days after they become certified in the REMS Program.

To ensure REMS participants' compliance with the REMS program, Juno Therapeutics, Inc. must:

8. Verify annually that the designated authorized representative for certified hospitals and their associated clinics 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: BREYANZI 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 are being met. Take corrective action if non-compliance is identified, including de-certification.
11. Maintain an ongoing annual audit plan of hospitals and their associated clinics.
12. Audit all certified hospitals and their associated clinics no later than 180 calendar days after the hospital places its first order of BREYANZI to ensure that all REMS processes and procedures are in place, functioning, and support the BREYANZI REMS Program requirements. Certified hospitals and their associated clinics must also be included in Juno Therapeutics, Inc.'s, ongoing annual audit plan.
13. Take reasonable steps to improve implementation of and compliance with the requirements in the BREYANZI REMS Program based on monitoring and evaluation of the BREYANZI REMS Program.

IV. REMS ASSESSMENT TIMETABLE

Juno Therapeutics, 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 REMS (XX/XX/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 calendar days before the submission date for that assessment. Juno Therapeutics, 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 BREYANZI REMS:

Enrollment Forms:

Health Care Setting:

1. [Hospital Enrollment Form](#)

Training and Educational Materials:

Patient:

2. [Patient Wallet Card](#)

Health Care Setting:

3. [Live Training Program](#)
4. [Knowledge Assessment](#)

Other Materials:

5. [REMS Program Website](#)

BREYANZI REMS Hospital Enrollment Form

BREYANZI is available only through BREYANZI REMS. Only hospitals and associated clinics certified in the BREYANZI REMS are permitted to dispense BREYANZI.

To become certified, hospitals and associated clinics must designate an Authorized Representative (AR) to:

1. Complete this enrollment form.
2. Oversee implementation and compliance with BREYANZI REMS requirements as outlined below.

BREYANZI Hospital and Associated Clinic Responsibilities

As a condition of certification, the certified hospital and associated clinics must:

- Ensure that if the hospital and 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/submit a new BREYANZI REMS Hospital Enrollment Form.
- Hospitals and their 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 to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088. Juno Therapeutics, Inc. is a Bristol-Myers Squibb Company.
- Dispense BREYANZI 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).
- 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.
- Comply with audits by Juno or a third party acting on behalf of Juno.

BREYANZI Authorized Representative Responsibilities

By signing this form, I attest that I am the AR designated by my institution to coordinate the activities of the BREYANZI REMS. I understand and agree to comply with the following BREYANZI REMS requirements:

- I have completed the BREYANZI REMS Live Training Program (live in-person or via webcast).
- I have submitted a completed BREYANZI REMS Knowledge Assessment to Juno online at BreyanziREMS.com, via email REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
- I will submit this 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.
- I will oversee my institution's implementation of and compliance with the BREYANZI REMS.
- I confirm, before administering BREYANZI, my institution has established processes and procedures that are subject to monitoring by Juno or a third party acting on behalf of Juno to help ensure compliance with the BREYANZI REMS requirements, including the following:
 - Ensure that 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 records are maintained of staff training.
 - Put processes and procedures in place to ensure that staff involved in prescribing, dispensing, or administering of BREYANZI are retrained on BREYANZI REMS if BREYANZI has not been dispensed at least once annually from the date of certification in the BREYANZI REMS.
 - Prior to dispensing BREYANZI, 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 infusing BREYANZI, provide patients with the Patient Wallet Card.

Authorized Representative Signature:

Date (MM/DD/YYYY):



BREYANZI REMS Hospital Enrollment Form

Complete all required fields and submit this enrollment form to Juno online at BreyanziREMS.com, via email REMSCallCenter@bms.com, or by fax to 1-855-496-8607.

Hospital Information (all fields required):

Hospital Name

Address

City

State

ZIP Code

Phone

Fax

Associated Clinic (if applicable):

Associated Clinic Name

Address

City

State

ZIP Code

Phone

Fax

Authorized Representative Information (all fields required):

First Name

Last Name

Job Title

Employee of

Hospital Associated Clinic

Credentials

MD DO PA RPh NP Other (please specify):

Phone

Fax

Work Email Address

Contact the REMS Call Center at 1-888-423-5436 or visit BreyanziREMS.com for more information.

Completion of this form and Knowledge Assessment does not guarantee that your institution will be certified to administer BREYANZI.

Juno will provide confirmation of BREYANZI REMS certification via email after processing this enrollment form and confirming that all other BREYANZI REMS requirements have been met.

Product orders cannot be placed until REMS certification is complete.



Information for Patient

BREYANZI may cause side effects that can lead to death.

Call your oncologist or go to the emergency room right away if the following symptoms appear:

- 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 heart rate
- Severe fatigue or weakness

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Patient Wallet Card

Have this card with you at all times. Show it to any doctor who sees you and when you go to the hospital.

- Tell any healthcare provider who sees you that you are being treated with BREYANZI®.
- For at least 4 weeks after receiving BREYANZI, you should plan to stay within 2 hours of the location where you received treatment.
- Refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after BREYANZI administration.

Name of BREYANZI Treating Oncologist

Office Phone Number

After-hours Phone Number

Hospital Name (for Management of BREYANZI Side Effects)

Date of BREYANZI Infusion

11/20 US-REMS-BRZ190003

BreyanziREMS.com

Information for the Healthcare Provider

This patient has received BREYANZI CAR T cell therapy, a CD19-directed genetically modified autologous T cell immunotherapy.



Following treatment with BREYANZI, Cytokine Release Syndrome (CRS) or neurologic toxicities may occur, which may be fatal or life-threatening. CRS may involve any organ system.

Contact Patient's Oncologist Immediately for Further Information and in the Following Situations:

- Before giving steroids or cytotoxic medications.
- If the patient has a serious infection.
- Before the patient undergoes an invasive procedure.



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 transaminases Grade 4	Grade 4 (excluding transaminases)

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.



BREYANZI® REMS Knowledge Assessment

All REMS-trained staff and Authorized Representatives (ARs) must complete this Knowledge Assessment. All questions must be answered correctly within 3 attempts. Completion of this Knowledge Assessment does not guarantee that your institution will be certified to administer BREYANZI.

You can take the Knowledge Assessment online at BreyanziREMS.com or by completing a paper copy. All Knowledge Assessments taken via paper must be submitted to the AR, who must send them to Juno via email at REMSCallCenter@bms.com, or via fax to 1-855-496-8607.

Knowledge Assessment Personnel Information (all fields required):

I am the AR Yes No

First Name _____ Last Name _____

Credentials
 MD DO PA RPh NP Other (please specify): _____

REMS Site ID: (if providing site ID, do not fill in address below)

Address

City _____ State _____ ZIP Code _____

Phone

Work Email Address

Signature _____ Date (MM/DD/YYYY) _____

To Be Completed by the Authorized Representative:

Please indicate what questions were answered correctly by writing yes (Y) or no (N) below.

Knowledge Assessment Attempt	Question										Total Grade (example: 7/10)
	1	2	3	4	5	6	7	8	9	10	
1											
2											
3											

All REMS-trained staff have 3 attempts to complete this Knowledge Assessment. After a third attempt, staff must repeat REMS Training before taking Knowledge Assessment again.

Continued on back

BREYANZI REMS Knowledge Assessment Questions

1. What is the approved indication for BREYANZI®?
- A. Relapsed or refractory (R/R) large B-cell lymphoma* after ≥2 lines of systemic therapy
 - B. Multiple myeloma
 - C. Primary central nervous system lymphoma
 - D. Newly diagnosed, untreated large B-cell lymphoma
2. Which of the following is true regarding the time to onset of CRS?
- A. With a median time to onset of 7 days
 - B. With a median time to onset of 5 days
 - C. With a median time to onset of 2 days
 - D. Rarely starts during the first week following BREYANZI infusion
3. All of the following regarding neurologic toxicity related to BREYANZI are correct except:
- A. Neurologic toxicity always occurs concurrently with CRS
 - B. Perform neurological work-up as appropriate to exclude other etiologies of neurological symptoms
 - C. The median time to onset of the first neurologic toxicity event is 8 days
 - D. The most common signs or symptoms of neurologic toxicity include encephalopathy, tremor, aphasia, and delirium
4. Every BREYANZI REMS-certified institution is required to have a minimum of 2 doses of tocilizumab on site for each patient prior to dispensing and administering BREYANZI:
- True
 - False
5. Delay infusion of BREYANZI if the patient has:
- A. Active uncontrolled infection
 - B. Active graft-versus-host disease
 - C. Unresolved serious adverse events from preceding chemotherapies
 - D. All of the above
 - E. A and C
6. A 75-year-old female with relapsed DLBCL treated with BREYANZI 6 days ago presents to the Emergency Room with a fever (39°C), myalgias, and mild hypotension that responded to an IV fluid bolus. What is/are the appropriate next step(s) in management?
- A. Evaluate the patient for febrile neutropenia/sepsis by obtaining blood and urine cultures, chest X-ray and complete blood count and start broad spectrum antibiotics
 - B. Admit the patient to the oncology ward and administer a dose of tocilizumab
 - C. Discharge the patient home to follow up the next day in the outpatient oncology clinic
 - D. A and B
7. Before BREYANZI infusion, patients should be given the BREYANZI Patient Wallet Card and be advised to:
- A. Refrain from driving or operating heavy or potentially dangerous machinery until at least 8 weeks following infusion
 - B. Remain within proximity of the certified healthcare facility for at least 4 weeks following the infusion
 - C. Seek immediate attention if they experience signs or symptoms of CRS and/or neurologic toxicities
 - D. All of the above
8. Clinically, BREYANZI patients with CRS can manifest the following signs and symptoms except:
- A. Hypotension
 - B. A fever of 100.4° Fahrenheit (38° Celsius) or higher
 - C. Hives
 - D. Chills or shaking chills
9. Four days after infusion of BREYANZI, a 70-year-old female with relapsed DLBCL develops the following signs and symptoms of CRS: fever (39°C), hypotension requiring intravenous fluids, and hypoxia requiring >40% FiO₂. 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
10. A 65-year-old male with relapsed DLBCL treated with BREYANZI 10 days ago presents to the outpatient clinic with moderate confusion and difficulty speaking that began an hour earlier at home. He did not have any preceding signs or symptoms of CRS since infusion. What is/are the appropriate next step/s in management:
- A. Obtain imaging of the head to evaluate for the possibility of stroke
 - B. Start tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg)
 - C. Start dexamethasone 10 mg intravenously every 12 to 24 hours
 - D. Consider non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis
 - E. All of the above except starting tocilizumab

* 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.



Risk Evaluation and Mitigation Strategy (REMS)

Boxed 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.

About BREYANZI REMS

A REMS 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. BREYANZI is available only under a restricted program called BREYANZI REMS because of the serious risks of CRS and neurologic toxicities.

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

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

BREYANZI REMS Requirements

All hospitals and their associated clinics must be certified and enrolled in the BREYANZI REMS to be able to infuse BREYANZI.

All relevant staff involved in the prescribing, dispensing, or administering of BREYANZI are trained on BREYANZI REMS requirements, and must successfully complete the BREYANZI REMS Knowledge Assessment.

Hospital and Associated Clinic Enrollment Instructions

To become certified to infuse BREYANZI, hospitals and associated clinics must designate an authorized representative (AR) to complete REMS requirements and enroll in BREYANZI REMS. The AR must:

1. Complete the BREYANZI REMS Live Training (live in-person or via webcast).
2. Successfully complete and submit a BREYANZI REMS Knowledge Assessment.
3. Oversee the implementation of and compliance with BREYANZI REMS to:
 - Ensure 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.
 - Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing, or administering of BREYANZI are retrained on BREYANZI REMS if BREYANZI has not been dispensed at least once annually from the date of certification in the BREYANZI REMS.
 - Dispense BREYANZI only after verifying a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for immediate administration (within 2 hours).
 - Prior to infusion, provide patients/caregivers with the Patient Wallet Card and instruct patients to remain within 2 hours of the certified hospital and its associated clinics for at least 4 weeks following BREYANZI infusion.
 - Ensure that, if the hospital and 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/submit a new BREYANZI REMS Enrollment Form.
4. Submit a completed BREYANZI REMS Enrollment Form online.

Report suspected adverse reactions to Bristol Myers Squibb at www.bms.com or 1-888-805-4555 or to the FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.

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.

Access BREYANZI online REMS training and Knowledge Assessment:

HEALTHCARE FACILITY STAFF >

Access BREYANZI REMS online resources:

AUTHORIZED REPRESENTATIVES >

CONTACT

For more information about BREYANZI REMS, call
1-888-423-5436.

RESOURCES

± BREYANZI Prescribing Information

± BREYANZI Medication Guide

± BREYANZI REMS Knowledge Assessment

± BREYANZI REMS Live Training Program

± BREYANZI REMS Patient Wallet Card

Risk Evaluation and Mitigation Strategy (REMS)

Boxed Warning

CYTOKINE RELEASE SYNDROME (CRS) and NEUROLOGIC TOXICITIES

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

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A REMS 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. BREVYANZ is available only under a restricted program called BREVYANZ REMS because of the serious risks of CRS and neurologic toxicities.

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 - Ensure all relevant staff involved in prescribing, dispensing, or administering of BREVYANZ are trained on the REMS requirements and successfully complete the BREVYANZ REMS Knowledge Assessment, and maintain records of staff training.
 - Put processes and procedures in place to ensure that staff involved in the prescribing, dispensing, or administering of BREVYANZ are retained on BREVYANZ REMS if BREVYANZ has not been dispensed at least once annually from the date of certification in the BREVYANZ REMS.
 - Dispense BREVYANZ only after verifying a minimum of 2 doses of tocilizumab are available on-site for each patient and ready for immediate administration (within 2 hours).
 - Prior to infusion, provide patients/caregivers with the Patient Relief Card and instruct patients to remain within 2 hours of the certified hospital and its associated clinics for at least 4 weeks following BREVYANZ infusion.
 - Ensure that, if the hospital and its associated clinic designate a replacement AR, the replacement AR must take the BREVYANZ REMS Live Training Program (in-person or via live webcast), complete the BREVYANZ REMS Knowledge Assessment, and complete/submit a new BREVYANZ REMS Enrollment Form.
 4. Submit a completed BREVYANZ REMS Enrollment Form online.
- Report successful enrollment reactions to Bristol Myers Squibb at www.bms.com or **1-800-805-4535** or to the FDA at www.fda.gov/medwatch or by calling **1-800-FDA-1088**.

Indication

BREVYANZ is a CD19-directed genetically modified subcutaneous 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 t(14q24) translocation), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 2B.

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

Access BREVYANZ online REMS training and Knowledge Assessment:

[MULTICARE FACILITY \(MFP\)](#)

Access BREVYANZ REMS online resources:

[CUSTOMER SUPPORT CENTER](#)

CONTACT

For more information about BREVYANZ REMS, call **1-800-423-5434**.

RESOURCES

- [BREVYANZ Prescribing Information](#)
- [BREVYANZ Instructions Guide](#)
- [BREVYANZ REMS Knowledge Assessment](#)
- [BREVYANZ REMS Live Training Program](#)
- [BREVYANZ REMS Patient Relief Card](#)

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Online REMS Training and Knowledge Assessment

For Healthcare Facility Staff

*Required

REMS Site ID *

No REMS Site ID? Please contact your DREYANZI REMS Authorized Representative.

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