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: 02/05/2021
Most Recent REMS Update: 06/2022

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 their 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:

<table>
<thead>
<tr>
<th>To become certified to dispense</th>
<th>1. Have a minimum of two doses of tocilizumab available on-site for each patient for immediate administration (within 2 hours of infusion).</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>3. Have the authorized representative complete the Live Training Program provided by the REMS Program.</td>
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<tr>
<td></td>
<td>4. Have the authorized representative successfully complete the Knowledge Assessment and submit it to the REMS Program.</td>
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<tr>
<td></td>
<td>5. Have the authorized representative enroll in the REMS Program by completing the Hospital Enrollment Form and submitting it to the REMS Program.</td>
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<tr>
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<td>6. Train all relevant staff involved in prescribing, dispensing, or administering of BREYANZI on the REMS Program requirements using the Live Training Program.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>
8. Establish processes and procedures to ensure relevant new staff involved in the prescribing, dispensing, or administration of BREYANZI are trained and complete the Knowledge Assessment and submit it to the REMS Program.

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 of infusion).

10. Establish processes and procedures to provide patients with the Patient Wallet Card.

<table>
<thead>
<tr>
<th>Before infusion</th>
<th>11. 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 of infusion) through the processes and procedures established as a requirement of the REMS Program.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before discharge</td>
<td>12. Provide the patient with the Patient Wallet Card through the processes and procedures established as a requirement of the REMS Program.</td>
</tr>
<tr>
<td>To maintain certification to dispense, if there is a change in authorized representative</td>
<td>13. Have a new Authorized Representative enroll in the REMS Program by completing the Hospital Enrollment Form.</td>
</tr>
<tr>
<td>To maintain certification to dispense, if BREYANZI has not been dispensed at least once annually from the date of initial certification in the REMS Program</td>
<td>14. Train all relevant staff involved in prescribing, dispensing, or administering of BREYANZI on the REMS Program requirements using the Live Training Program.</td>
</tr>
<tr>
<td></td>
<td>15. Have all relevant staff involved in prescribing, dispensing, or administering of BREYANZI successfully complete the Knowledge Assessment.</td>
</tr>
<tr>
<td>At all times</td>
<td>16. Report any serious(^1) adverse events suggestive of CRS or neurological toxicities to the REMS Program.</td>
</tr>
<tr>
<td></td>
<td>17. Maintain records of staff training.</td>
</tr>
<tr>
<td></td>
<td>18. Maintain records that processes and procedures are in place and are being followed.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>

2. Patients who are prescribed BREYANZI:

| Before discharge                      | 1. Receive the Patient Wallet Card.                                                                                                           |

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\(^1\) For the purpose of this REMS, 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 the 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 online via e-mail and fax.
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 the 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 (02/05/2021). 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:

   Healthcare Setting:
   1. Hospital Enrollment Form

Training and Educational Materials:

   Patient:
   2. Patient Wallet Card

   Healthcare Setting:
   3. Live Training Program
   4. Knowledge Assessment

Other Materials:

   5. REMS Program Website
BREYANZI® REMS Hospital Enrollment Form

BREYANZI is available only through the BREYANZI REMS. Only hospitals and their associated clinic(s) certified in the BREYANZI REMS are permitted to dispense BREYANZI.

To become certified, hospitals and their associated clinic(s) must designate an authorized representative (AR) to:

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

BREYANZI Hospital and Associated Clinic Responsibilities

As a condition of certification, the certified hospitals and their associated clinic(s) must:

- Ensure that when the hospitals and their associated clinic(s) designate an AR, the AR must take the Training Program, successfully complete the Knowledge Assessment, and complete and submit a new Hospital Enrollment Form.
- Report any serious* adverse events suggestive of cytokine release syndrome (CRS) or neurologic toxicities to Juno Therapeutics, Inc., a Bristol-Myers Squibb Company, at www.bms.com or 1-888-805-4555, or to FDA at www.fda.gov/medwatch or by calling 1-800-FDA-1088.
- 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 of BREYANZI infusion).
- Before discharge, provide the patient with the Patient Wallet Card.
- Maintain documentation of all processes and procedures for the BREYANZI REMS and provide documentation upon request to Juno Therapeutics, Inc. or to a third party acting on behalf of Juno Therapeutics, Inc.
- Comply with audits by Juno Therapeutics, Inc. or a third party acting on behalf of Juno Therapeutics, Inc.

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 Training Program and successfully completed the Knowledge Assessment.
- I have submitted a completed BREYANZI REMS Knowledge Assessment to the BREYANZI REMS online at BreyanziREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
- I will submit this completed BREYANZI REMS Hospital Enrollment Form to the BREYANZI REMS online at BreyanziREMS.com, via email to 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 requirements.
- I confirm, before administering BREYANZI, that my institution has established processes and procedures that are subject to monitoring by Juno Therapeutics, Inc. or a third party acting on behalf of Juno Therapeutics, Inc. 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 using the Training Program, and successfully complete and submit the 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 the BREYANZI REMS if BREYANZI has not been dispensed at least once annually from the date of certification in the BREYANZI REMS or the last order date of BREYANZI.
  - 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 of infusion).
  - Before discharge, provide patients with the Patient Wallet Card.

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.

*Authorized Representative Signature: ____________________________ Date (MM/DD/YYYY): ____________________________
Complete all required fields and submit this enrollment form to the BREYANZI REMS online at BreyanziREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.

### Hospital Information (all fields required):

**Hospital Name**

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

<table>
<thead>
<tr>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>City</td>
</tr>
</tbody>
</table>

| Phone   | Fax   |

### Associated Clinic (if applicable):

**Associated Clinic Name**

<table>
<thead>
<tr>
<th>Address</th>
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</thead>
<tbody>
<tr>
<td>City</td>
</tr>
</tbody>
</table>

| Phone   | Fax   |

### Authorized Representative Information (all fields required):

**First Name**    **Last Name**

**Job Title**    **Employee of**

- ○ Hospital  ○ Associated Clinic

<table>
<thead>
<tr>
<th>Credentials</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ MD</td>
</tr>
</tbody>
</table>

| Phone   | Fax   |

**Work Email Address**

Contact the REMS Call Center at 1-888-423-5436 or visit www.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 Therapeutics, Inc. will provide confirmation of the 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 are life-threatening and 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

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.
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:

- The administration of steroids or cytotoxic medications.
- If the patient has a serious infection.
- Any planned invasive procedure(s) for the patient.

Information for the Healthcare Provider

www.BreyanziREMS.com
BREYANZI® REMS Training Program
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 large B-cell lymphoma (LBCL), 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, who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- relapsed or refractory disease after two or more lines of systemic therapy

Limitations of Use: BREYANZI is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.

Please see full Prescribing Information including Boxed WARNINGS and Medication Guide.
BREYANZI® REMS Overview
About the 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 the 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 their 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 Their Associated Clinic(s)

To become certified to dispense BREYANZI®, hospitals and associated clinic(s) must:

1. Designate an authorized representative (AR) to carry out the certification process by completing and submitting the Hospital Enrollment Form on behalf of the hospital and its associated clinic(s).

2. Ensure the AR oversees implementation and compliance with the 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 of infusion).

4. Ensure that if the hospital or its associated clinic(s) designate a replacement AR, the replacement AR must take the Training Program, complete the Knowledge Assessment, and complete and submit a new Hospital Enrollment Form.
Certification of Hospitals and Their Associated Clinic(s) (cont’d)

5. Maintain documentation of all processes and procedures for the BREYANZI® REMS and provide documentation upon request to Juno Therapeutics, Inc., a Bristol-Myers Squibb Company, or to a third party acting on behalf of Juno Therapeutics, Inc.

6. Comply with audits 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 for the BREYANZI REMS.

7. Report any serious adverse events suggestive of CRS or neurologic toxicities to Bristol-Myers Squibb Company 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.

- For the purpose of this REMS, 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. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Identifying an Authorized Representative

The AR responsible for the hospital and any associated clinic(s) must have capacity to oversee implementation of, and compliance with, the BREYANZI® REMS by:

1. Ensuring that all relevant staff are trained, complete the Knowledge Assessment, and maintain records.

2. Having the ability to ensure that processes and procedures have been established and are being followed.

3. Having the ability to comply with audits carried out by Juno Therapeutics, Inc.

It is not required that the AR be a healthcare provider.
Responsibilities of the BREYANZI® REMS Authorized Representative

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

- Complete the BREYANZI REMS Live Training Program (live in-person, via webcast or online), which includes review of:
  - REMS Training Program
- Oversee the implementation of, and compliance with, the BREYANZI REMS in hospitals and associated clinic(s).
- Submit a successfully completed BREYANZI REMS Knowledge Assessment to the BREYANZI REMS online at www.BreyanziREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
- Submit a successfully completed BREYANZI REMS Hospital Enrollment Form to the BREYANZI REMS online at www.BreyanziREMS.com, via email to REMSCallCenter@bms.com, or by fax to 1-855-496-8607.
Responsibilities of the BREYANZI® REMS Authorized Representative (cont’d)

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

- All relevant staff involved in prescribing, dispensing, or administering of BREYANZI are trained on the REMS requirements using the Training Program, and successfully complete and submit the Knowledge Assessment, and records are maintained of staff training (including a retraining process 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 of BREYANZI infusion).

- Before discharge, provide patients with the Patient Wallet Card.
Completion of the BREYANZI® REMS Training and Knowledge Assessment

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

- Individuals involved in prescribing, dispensing, or administering BREYANZI.
- Individuals who will be the AR or may complete tasks on behalf of the AR.
- Individuals who may discuss the BREYANZI REMS education with patients or provide a Patient 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 Therapeutics, Inc. recognizes that the assignment of REMS activities may be made to different personnel in each healthcare facility. Each healthcare facility should independently assess REMS training needs to ensure that appropriate personnel are trained.
Serious Risks 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®. Among patients receiving BREYANZI for LBCL (N=418), CRS occur in 46% (190/418), including ≥ Grade 3 CRS (Lee grading system) in 3.1% of patients.

- In patients receiving BREYANZI after two or more lines of therapy for LBCL, CRS occurred in 46% (122/268), including ≥ Grade 3 CRS in 4.1% of patients. One patient had fatal CRS and 2 had ongoing CRS at time of death. The median time to onset was 5 days (range: 1 to 15 days). CRS resolved in 98% with a median duration of 5 days (range: 1 to 17 days).

- In patients receiving BREYANZI after one line of therapy for LBCL, CRS occurred in 45% (68/150), including Grade 3 CRS in 1.3% of patients. The median time to onset was 4 days (range: 1 to 63 days). CRS resolved in all patients with a median duration of 4 days (range: 1 to 16 days).

- The most common manifestations of CRS (≥10%) included fever (94%), hypotension (42%), tachycardia (28%), chills (23%), hypoxia (16%), and headache (12%).

- Serious events that may be associated with CRS include cardiac arrhythmias (including atrial fibrillation and ventricular tachycardia), cardiac arrest, cardiac failure, diffuse alveolar damage, renal insufficiency, capillary leak syndrome, hypotension, hypoxia, and hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS).

- Ensure that 2 doses of tocilizumab are available prior to infusion of BREYANZI.

- Of the 418 patients who received BREYANZI for LBCL, 23% received tocilizumab and/or a corticosteroid for CRS, including 10% who received tocilizumab only and 2.2% who received corticosteroids only.

- Monitor patients daily for at least 7 days following BREYANZI infusion at a REMS-certified healthcare facility for signs and symptoms of CRS. Monitor patients for signs or symptoms of CRS for at least 4 weeks after infusion. At the first sign of CRS, institute treatment with supportive care, tocilizumab, or tocilizumab and corticosteroids as indicated.

- Counsel patients to seek immediate medical attention should signs or symptoms of CRS occur at any time.

Approved v1.0
Managing CRS

- Identify CRS based on clinical presentation.
- Evaluate for and treat other causes of fever, hypoxia, and hypotension.
- Monitor patients daily for at least 7 days following BREYANZI® infusion at a REMS-certified healthcare facility 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 proximity of the certified healthcare facility for at least 4 weeks following infusion.
- If CRS is suspected, manage according to the recommendations on slides 18-19.
- 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 18-19 and slides 24-25 respectively.
  - Tocilizumab according to the CRS grade on slides 18-19.
  - Antiseizure medication according to the neurologic toxicity on slides 24-25.
Lee Criteria\(^1\) 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.

<table>
<thead>
<tr>
<th>Symptoms/Signs</th>
<th>CRS Grade 1 (mild)</th>
<th>CRS Grade 2 (moderate)</th>
<th>CRS Grade 3 (severe)</th>
<th>CRS Grade 4 (life-threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Yes</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td>Systolic blood pressure (SBP) ≤90 mmHg</td>
<td>N/A</td>
<td>Responds to IV fluids or single low-dose vasopressor</td>
<td>Needs high-dose or multiple vasopressors</td>
<td>Life-threatening</td>
</tr>
<tr>
<td>Need for oxygen to reach oxygen saturation (SaO(_2)) &gt;90%</td>
<td>N/A</td>
<td>Fraction of inspired oxygen (FiO(_2)) ≤40%</td>
<td>FiO(_2) ≥40%</td>
<td>Needs ventilator support</td>
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<tr>
<td>Organ toxicity</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>N/A</td>
<td>Grade 2</td>
<td>Grade 3 or transaminitis Grade 4</td>
<td>Grade 4 (excluding transaminitis)</td>
</tr>
</tbody>
</table>

CRS grade is defined by the most severe of the symptoms listed below, excluding fever (i.e., SBP, oxygen requirement, and organ toxicity).

FiO\(_2\), fraction of inspired oxygen; IV, intravenous; SaO\(_2\), oxygen saturation.
## BREYANZI® CRS Grading and Management Guidance

<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>When to use tocilizumab</th>
<th>When to use corticosteroids†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>If &lt;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.</td>
<td>If &lt;72 hours after infusion, consider dexamethasone 10 mg IV every 24 hours. If ≥72 hours after infusion, treat symptomatically.</td>
</tr>
<tr>
<td>Fever</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.

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<tbody>
<tr>
<td>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.</td>
<td>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.</td>
<td>If &lt;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.</td>
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</tr>
</tbody>
</table>

IV, intravenous; FiO$_2$, 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.
### BREYANZI® CRS Grading and Management Guidance (cont’d)

<table>
<thead>
<tr>
<th>CRS Grade*</th>
<th>When to use tocilizumab</th>
<th>When to use corticosteroids†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3</td>
<td>Per Grade 2.</td>
<td>Administer dexamethasone 10 mg IV every 12 hours.</td>
</tr>
<tr>
<td>Symptoms require and respond to aggressive intervention. Oxygen requirement ≥40% FiO₂, or hypotension requiring high-dose or multiple vasopressors, or Grade 3 organ toxicity, or Grade 4 transaminitis.</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

| Grade 4    | Per Grade 2.            | Administer dexamethasone 20 mg IV every 6 hours. |
| Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous hemodialysis (CVVHD) or Grade 4 organ toxicity (excluding transaminitis). | 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. |

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.
Management of Neurologic Toxicities
Clinical Presentation of Neurologic Toxicities

- Neurologic toxicities that were fatal or life-threatening, including immune effector cell-associated neurotoxicity syndrome (ICANS), occurred following treatment with BREYANZI®. Serious events including cerebral edema and seizures occurred with BREYANZI. Fatal and serious cases of leukoencephalopathy, some attributable to fludarabine, also occurred.

- In patients receiving BREYANZI after two or more lines of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred in 35% (95/268), including ≥ Grade 3 cases in 12% of patients. Three patients had fatal neurologic toxicity and 7 had ongoing neurologic toxicity at time of death. The median time to onset of neurotoxicity was 8 days (range: 1 to 46 days). Neurologic toxicities resolved in 85% with a median duration of 12 days (range: 1 to 87 days).

- In patients receiving BREYANZI after one line of therapy for LBCL, CAR T cell-associated neurologic toxicities occurred in 27% (41/150) of patients, including Grade 3 cases in 7% of patients. The median time to onset of neurologic toxicity was 8 days (range: 1 to 63 days). The median duration of neurologic toxicity was 6 days (range: 1 to 119 days).

- In all patients combined receiving BREYANZI for LBCL, neurologic toxicities occurred in 33% (136/418), including ≥ Grade 3 cases in 10% of patients. The median time to onset was 8 days (range: 1 to 63), with 87% of cases developing by 16 days. Neurologic toxicities resolved in 85% of patients with a median duration of 11 days (range: 1 to 119 days). Of patients developing neurotoxicity, 77% (105/136) also developed CRS.

- The most common neurologic toxicities (≥5%) included encephalopathy (20%), tremor (13%), aphasia (8%), headache (6%), dizziness (6%), and delirium (5%).

- Monitor patients daily for at least 7 days following BREYANZI infusion at a REMS-certified healthcare facility for signs and symptoms of neurologic toxicities and assess for other causes of neurological symptoms. Monitor patients for signs or symptoms of neurologic toxicities for at least 4 weeks after infusion and treat promptly. Manage neurologic toxicity with supportive care and/or corticosteroid as needed.

- Counsel patients to seek immediate medical attention should signs or symptoms of neurologic toxicity occur at any time.

- 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

- Monitor patients for signs and symptoms of neurologic toxicities.
- Rule out other causes of neurologic symptoms.
- If neurologic toxicity is suspected, manage according to the recommendations on slides 24-25.
- 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 18-19 and 24-25.
  - Tocilizumab according to the CRS grade on slides 18-19.
  - Antiseizure medication according to the neurologic toxicity on slides 24-25.
- Provide intensive care supportive therapy for severe or life-threatening neurologic toxicities.
- Monitor patients daily for at least 7 days following BREYANZI® infusion at a REMS-certified healthcare facility 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

<table>
<thead>
<tr>
<th>Adverse event term/Neurotoxicity domain²</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral edema</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Confusion</td>
<td>Mild disorientation</td>
<td>Moderate disorientation; limiting instrumental ADL</td>
<td>Severe disorientation; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Depressed level of consciousness</td>
<td>Decreased level of alertness</td>
<td>Sedation; slow response to stimuli; limiting instrumental ADL</td>
<td>Difficult to arouse</td>
<td>Life-threatening consequences</td>
</tr>
<tr>
<td>Dysphasia</td>
<td>Awareness of receptive or expressive characteristics; not impairing ability to communicate</td>
<td>Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously</td>
<td>Severe receptive or expressive characteristics; impairing ability to read, write, communicate intelligibly</td>
<td>N/A</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Headache</td>
<td>Mild pain</td>
<td>Moderate pain; limiting instrumental ADL</td>
<td>Severe pain; limiting self-care ADL</td>
<td>N/A</td>
</tr>
<tr>
<td>Seizure</td>
<td>Brief partial seizure; no loss of consciousness</td>
<td>Brief generalized seizure</td>
<td>Multiple seizures despite medical intervention</td>
<td>Life-threatening; prolonged repetitive seizures</td>
</tr>
<tr>
<td>Tremor</td>
<td>Mild symptoms</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL</td>
<td>N/A</td>
</tr>
</tbody>
</table>

ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events.
# Neurologic Toxicity Grading and Management Guidance

<table>
<thead>
<tr>
<th>NT Grade*</th>
<th>Corticosteroids and Antiseizure Medication</th>
</tr>
</thead>
</table>
| **Grade 1** | Start non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.  
If ≥72 hours after infusion, observe.  
If <72 hours after infusion, consider dexamethasone 10 mg IV every 12 to 24 hours for 2 to 3 days. |
| **Grade 2** | Start non-sedating, antiseizure medicines (eg, levetiracetam) for seizure prophylaxis.  
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.  
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.  
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). |

IV, intravenous; NT, neurologic toxicity.  
* NCI CTCAE criteria for grading neurologic toxicities version 4.03.
# Neurologic Toxicity Grading and Management Guidance

<table>
<thead>
<tr>
<th>NT Grade*</th>
<th>Corticosteroids and Antiseizure Medication</th>
</tr>
</thead>
</table>
| **Grade 3** | Start non-sedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis.  
Dexamethasone 10 to 20 mg IV every 8 to 12 hours. Steroids are not recommended for isolated Grade 3 headaches.  
If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2).  
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. |
| **Grade 4** | Start non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.  
Dexamethasone 20 mg IV every 6 hours.  
If no improvement after 24 hours or worsening of neurologic toxicity, escalate to methylprednisolone (dose and frequency as per Grade 2).  
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. |

IV, intravenous; NT, neurologic toxicity.  
* NCI 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.

- Report any serious adverse events suggestive of CRS or neurologic toxicities to Bristol-Myers Squibb Company 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.

  - For the purpose of this REMS, 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. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
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

• Advise the patient to read the FDA-approved patient labeling (Medication Guide).

• 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).

• Before discharge, 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 Company 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


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

<table>
<thead>
<tr>
<th>Knowledge Assessment Attempt</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>Total Grade (example: 7/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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</tbody>
</table>

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.
1. BREYANZI (lisocabtagene maraleucel) is indicated for the treatment of adult patients with large B-cell lymphoma (LBCL)* who have:

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy
- Refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age
- Relapsed or refractory disease after two or more lines of systemic therapy
- All of the above

2. Which of the following is true regarding the time to onset of cytokine release syndrome (CRS)?

- With a median time to onset of 6-7 days
- With a median time to onset of 4-5 days
- Rarely starts during the first week following BREYANZI infusion

3. All of the following regarding neurologic toxicity related to BREYANZI are correct except:

- Neurologic toxicity always occurs concurrently with CRS
- Perform neurological work-up as appropriate to exclude other etiologies of neurological symptoms
- The median time to onset of the first neurologic toxicity event is 8 days
- 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:

- Active uncontrolled infection
- Active graft-versus-host disease
- All of the above
- None of the above

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 hypotension that responded to an IV fluid bolus. What is/are the appropriate next step(s) in management?

- 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
- Admit the patient to the oncology ward and administer a dose of tocilizumab
- Discharge the patient home to follow up the next day in the outpatient oncology clinic
- A and B

7. Before discharge, patients should be given the BREYANZI Patient Wallet Card and be advised to:

- Refrain from driving or operating heavy or potentially dangerous machinery until at least 8 weeks following infusion
- Remain within 2 hours of the certified healthcare facility for at least 4 weeks following the infusion
- Seek immediate attention if they experience signs or symptoms of CRS and/or neurologic toxicities
- All of the above

8. Clinically, BREYANZI patients with CRS can manifest the following signs and symptoms except:

- Hypotension
- A fever of 100.4° Fahrenheit (38° Celsius) or higher
- Hives
- 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:

- Grade 1 CRS
- Grade 2 CRS
- Grade 3 CRS
- 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:

- Obtain imaging of the head to evaluate for the possibility of stroke
- Start tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg)
- Start dexamethasone 10 mg intravenously every 12 to 24 hours
- Consider nonsedating, antiseizure medicines (e.g., levetiracetam) for seizure prophylaxis
- All of the above except starting tocilizumab

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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 a history of CRS, inflammatory disorders, or active infections. 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 strokes, convulsions, seizures, and coma. Monitor for neurologic events after treatment with Breyanzi. Provide supportive care and cardiovascular monitor 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 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 available only 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:
1. Ensuring that hospitals and their associated clinic(s) that dispense Breyanzi are staffed and equipped to handle serious complications.
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 clinic(s) must be certified and enrolled in the Breyanzi REMS to be eligible to infuse Breyanzi. All staff involved in the prescribing, dispensing, or administering of Breyanzi are trained in the Breyanzi REMS requirements and must complete the Knowledge Assessment and submit it to the REMS Program.

**Hospital and Associated Clinic Enrollment Instructions**
To become certified to infuse Breyanzi, hospitals and their associated clinic(s) must designate an authorized representative (AR) to complete REMS requirements and enroll in the Breyanzi REMS. The AR must:
1. Complete the Breyanzi REMS Training Program (live in-person, via webcast, or online), which includes:
   - REMS Training Program
2. Successfully complete the Knowledge Assessment and submit it to the REMS Program.
3. Ongoing implementation and compliance with the Breyanzi REMS requirements to:
   - Ensure all relevant staff involved in prescribing, dispensing, or administering of Breyanzi are trained on the REMS requirements using the Training Program, and successfully complete and submit the Knowledge Assessment, and are maintained on staff training.
   - Provide procedures and processes to ensure that staff involved in the prescribing, dispensing, or administering of Breyanzi are retrained on the Breyanzi REMS if Breyanzi has not been administered 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 of infusion).
   - Before discharge, provide patients/caregivers with the Patient Wallet Card and instruct patients to remain within 2 hours of the certified healthcare facility for at least 4 weeks following Breyanzi infusion.
4. Ensure that when the hospital and its associated clinic(s) designate an AR, the AR must complete the Training Program, successfully complete the Knowledge Assessment, and complete and submit a new Hospital Enrollment Form.

Report suspected adverse reactions to Breyanzi to either the FDA at 1-888-260-4558 or to the FDA at www.fda.gov, or to the FDA at 1-888-260-4558 or to the FDA at www.fda.gov/medwatch by calling 1-800-FDA-1088. (Requires time to process).

**Indication**
Breyanzi is a CD19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including DLBCL (diffuse large B-cell lymphoma [DLBCL]), not otherwise specified (NOS) (including DLBCL arising from localized lymphomas), high-grade B-cell lymphomas, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B, who have:
- refractory disease to frontline chemotherapy or relapse within 12 months of frontline chemotherapy; or
- refractory disease to frontline chemotherapy or relapse after frontline chemotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or
- relapsed or refractory disease after two or more lines of systemic therapy.

Limitations of Use (Breyanzi) is not indicated for the treatment of patients with primary central nervous system (CNS) lymphomas.
Approved
1.0
v