

# Risk Evaluation and Mitigation Strategy (REMS) Document

## ZULRESSO (brexanolone) REMS Program

### I. Administrative Information

Application Number: NDA 211371  
Application Holder: Sage Therapeutics, Inc.  
Initial REMS Approval: 03/2019  
Most Recent REMS Update: 12/2019

### II. REMS Goal

The goal of the ZULRESSO REMS Program is to mitigate the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the ZULRESSO infusion by:

- i. Ensuring that ZULRESSO is administered only to patients in a medically supervised setting that provides monitoring while ZULRESSO is administered.
- ii. Ensuring pharmacies and healthcare settings that dispense ZULRESSO are certified.
- iii. Ensuring that each patient is informed of the adverse events of excessive sedation and loss of consciousness and the need for monitoring while ZULRESSO is administered.
- iv. Enrollment of all patients in a registry to characterize the risks and support safe use.

### III. REMS Requirements

**Sage Therapeutics, Inc. must ensure that healthcare settings, patients, pharmacies, and wholesalers-distributors comply with the following requirements:**

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#### 1. Healthcare settings that dispense ZULRESSO must:

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| To become certified to dispense | <ol style="list-style-type: none"><li>1. Be able to monitor patients continuously for the duration of the infusion.</li><li>2. Have the following onsite: continuous pulse oximetry, fall precaution protocol, intravenous programmable infusion pumps with alarms to alert when the pump malfunctions, healthcare providers to continuously monitor patients and intervene as necessary.</li><li>3. Designate an Authorized Representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the healthcare setting.</li><li>4. Have the Authorized Representative review the <a href="#">Training for Healthcare Settings</a>.</li></ol> |
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5. Have the Authorized Representative successfully complete the [Healthcare Setting Knowledge Assessment](#) and submit it to the REMS Program.
  6. Have the Authorized Representative enroll in the REMS Program by completing the [Healthcare Setting Enrollment Form](#) and submitting it to the REMS Program.
  7. Train all relevant staff involved in prescribing, dispensing, and administering ZULRESSO on the REMS Program requirements using the [Training for Healthcare Settings](#).
  8. Establish processes and procedures to identify new staff involved in prescribing, dispensing, and administering ZULRESSO and ensure they are trained.
  9. Establish processes and procedures to enroll the patient in the REMS program.
  10. Establish processes and procedures to counsel the patient and verify the patient is enrolled in the REMS Program before administration.
  11. Establish processes and procedures to submit the [Post Infusion Form](#) and [Excessive Sedation and Loss of Consciousness Adverse Event Form](#) to the REMS Program.
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Before dispensing

12. Enroll the patient by completing and submitting the [Patient Enrollment Form](#) to the REMS Program.
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Before administering

13. Verify the patient is enrolled through the processes and procedures established as a requirement of the REMS Program.
  14. Counsel the patient on signs and symptoms of excessive sedation, loss of consciousness, and the importance of immediately reporting to a healthcare provider any signs and symptoms of excessive sedation using the [Patient Information Guide](#). Provide a copy of the material to the patient.
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During treatment, every 2 hours

15. Assess the patient's health status for signs and symptoms of excessive sedation and loss of consciousness.
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During treatment

16. Assess the patient's oxygen saturation using continuous pulse oximetry.
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After treatment discontinuation, prior to discharge

17. Assess the patient's level of sedation.
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After treatment discontinuation, within 3 business days of completion date	<p>18. Document and submit to the REMS Program using the <a href="#">Post Infusion Form</a>.</p> <p>19. Report excessive sedation or loss of consciousness to the REMS Program using the <a href="#">Excessive Sedation and Loss of Consciousness Adverse Event Form</a>.</p>
To maintain certification to dispense	20. Have any new Authorized Representative enroll in the REMS Program by successfully completing the <a href="#">Healthcare Setting Knowledge Assessment</a> and the <a href="#">Healthcare Setting Enrollment Form</a> and submitting both to the REMS Program.
At all times	<p>21. Not distribute, transfer, loan, or sell ZULRESSO.</p> <p>22. Maintain records documenting staff's completion of training.</p> <p>23. Maintain records that all REMS processes and procedures are in place and are being followed.</p> <p>24. Maintain records of all shipments of ZULRESSO received and dispensing information including patient name, dose, number of vials, and date administered for all patients.</p> <p>25. Comply with audits carried out by Sage Therapeutics, Inc. or third party acting on behalf of Sage Therapeutics, Inc. to ensure that all processes and procedures are in place and are being followed.</p>

## 2. Patients who are prescribed ZULRESSO:

Before treatment initiation	<p>1. Review the <a href="#">Patient Information Guide</a> with a healthcare provider.</p> <p>2. Enroll in the REMS Program by completing the <a href="#">Patient Enrollment Form</a> with a healthcare provider. Enrollment information will be provided to the REMS Program.</p> <p>3. Receive counseling from a healthcare provider on the adverse events of loss of consciousness and signs and symptoms of excessive sedation.</p>
During treatment	<p>4. Be monitored for excessive sedation and loss of consciousness.</p> <p>5. Report any symptoms of excessive sedation to a healthcare provider.</p>

## 3. Pharmacies that dispense ZULRESSO must:

To become certified to dispense	1. Designate an authorized representative to carry out the certification process and oversee implementation and compliance with the REMS Program on behalf of the pharmacy.
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2. Have the authorized representative review the Program Overview.
  3. Have the authorized representative enroll in the REMS Program by completing the Pharmacy Enrollment Form and submitting it to the REMS Program.
  4. Train all relevant staff involved in dispensing that ZULRESSO must only be dispensed to a certified healthcare setting.
  5. Establish processes and procedures to verify the healthcare setting is certified in the REMS Program.

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Before dispensing

6. Verify that the healthcare setting is certified through the processes and procedures established as a requirement of the REMS Program.

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At all times

7. Not distribute, transfer, loan or sell ZULRESSO.
8. Maintain records documenting staff's completion of training.
9. Maintain records that all REMS processes and procedures are in place and are being followed.
10. Maintain records of all shipments of ZULRESSO received and dispensing information including patient name, dose, and number of vials.
11. Comply with audits carried out by Sage Therapeutics, Inc. or third party acting on behalf of Sage Therapeutics to ensure that all processes and procedures are in place and are being followed.

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#### **4. Wholesalers-distributors that distribute ZULRESSO must:**

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To be able to distribute

1. Establish processes and procedures to distribute only to certified healthcare settings and pharmacies.
2. Train all relevant staff involved in distributing on the REMS Program requirements.

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At all times

3. Distribute only to certified healthcare settings and pharmacies.
4. Maintain records of drug distribution.
5. Maintain records that all processes and procedures are in place and are being followed.
6. Comply with audits carried out by Sage Therapeutics, Inc. or a third party acting on behalf of Sage Therapeutics, Inc. to ensure all processes and procedures are in place and being followed.

**Sage Therapeutics, Inc. must provide training to healthcare settings that dispense ZULRESSO.**

The training includes the following educational materials: [Training for Healthcare Settings](#) and [Healthcare Setting Knowledge Assessment](#). The training must be available online and in hard copy format.

**Sage Therapeutics, Inc. must provide training to pharmacies that dispense ZULRESSO.**

The training includes the following educational material: [Program Overview](#). The training must be available online and in hard copy format.

**To inform healthcare providers about the REMS Program and the risks and safe use of ZULRESSO, Sage Therapeutics, Inc must disseminate REMS communication materials according to the table below:**

<b>Target Audience</b>	<b>Communication Materials &amp; Dissemination Plan</b>
Healthcare providers likely to prescribe ZULRESSO	REMS Letter: <a href="#">Letter for Healthcare Providers</a> with attachment: <a href="#">Patient Information Guide</a> <ol style="list-style-type: none"><li>1. Email within 60 calendar days of the date ZULRESSO is first commercially distributed and again 12 months later.<ol style="list-style-type: none"><li>a. Send by mail within 30 calendar days of the date the first email was sent if a healthcare provider’s email address is not available or the email is undeliverable.</li><li>b. Send a second email within 30 calendar days of the date of the first email sent if the first email is marked unopen.</li></ol></li><li>2. Disseminate through field-based sales and medical representatives.</li></ol>

**To support REMS Program operations, Sage Therapeutics, Inc. must:**

1. Establish and maintain a REMS Program Website, [www.zulressorems.com](http://www.zulressorems.com). The REMS Program Website must include the option to print the prescribing information and REMS materials. All product websites for consumers and healthcare providers must include prominent REMS-specific links to the REMS Program website. The REMS Program Website must not link back to the promotional product website(s).
2. Make the REMS Program Website fully operational and all REMS materials available through the website and call center by the date ZULRESSO is first commercially distributed.
3. Establish and maintain a REMS Program coordinating center for REMS participants at 844-472-4379 and [information@zulressorems.com](mailto:information@zulressorems.com).
4. Establish and maintain a validated, secure database of all REMS participants who are enrolled and/or certified in the REMS Program.
5. Ensure healthcare settings and pharmacies are able to enroll online, by email, and fax.
6. Ensure healthcare providers are able to enroll patients by email and fax.
7. Ensure wholesalers-distributors and pharmacies are able to verify enrollment/certification status by phone.
8. Ensure healthcare settings are able to verify enrollment/certification status by phone and online.

9. Ensure healthcare providers are able to submit the [Post Infusion Form](#) and [Excessive Sedation and Loss of Consciousness Adverse Event Form](#) by email, fax, and online.
10. Provide the [Training for Healthcare Settings](#), [Healthcare Setting Knowledge Assessment](#), [Healthcare Setting Enrollment Form](#), [Post Infusion Form](#), [Excessive Sedation and Loss of Consciousness Adverse Event Form](#), [Program Overview](#), [Pharmacy Enrollment Form](#), [Patient Information Guide](#), [Patient Enrollment Form](#), and the Prescribing Information to REMS participants who (1) attempt to dispense or administer ZULRESSO and are not yet certified or (2) inquire about how to become certified.
11. Notify healthcare settings and pharmacies within 2 business days after they become certified in the REMS Program.
12. Provide public access to a database of certified healthcare settings and pharmacies.
13. Provide certified pharmacies access to the database of certified healthcare settings and authorized wholesalers-distributors.
14. Provide certified healthcare settings access to the database of certified pharmacies, enrolled patients, and authorized wholesalers-distributors.
15. Provide authorized wholesalers-distributors access to the database of certified pharmacies and healthcare settings.
16. Establish and maintain a registry which includes a reporting and collection system for all patients to provide information on the incidence of excessive sedation and loss of consciousness.
17. Ensure that once a report suggestive of excessive sedation and loss of consciousness is received, Sage Therapeutics, Inc. follows up with the healthcare provider to obtain all required data for the registry.

**To ensure REMS participants' compliance with the REMS Program, Sage Therapeutics, Inc. must:**

18. Verify annually that the designated authorized representative for the healthcare setting or pharmacy is the same. If different, the healthcare setting or pharmacy must re-certify with a new authorized representative.
19. Notify healthcare settings if a completed Post Infusion Form has not been received by the REMS Program within 3 business days from the date of the patient completing the infusion or the scheduled infusion completion date. If the [Post Infusion Form](#) is not received within 15 business days, Sage will contact the authorized representative. If the form is not received within 30 business days, Sage will investigate on site.
20. Notify healthcare settings if a completed [Excessive Sedation and Loss of Consciousness Adverse Event Form](#) is required and not received within 15 business days from receipt of the [Post Infusion Form](#). If the form is not received within 30 business days, Sage will investigate.
21. Maintain adequate records to demonstrate that REMS requirements have been met, including, but not limited to records of: drug distribution and dispensing; certification of healthcare settings and pharmacies; enrolled patients; and audits of REMS participants. These records must be readily available for FDA inspections.
22. Establish a plan for addressing noncompliance with REMS Program requirements.
23. Monitor pharmacies and healthcare settings 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.

24. Audit 10% but no less than 50 certified healthcare settings and certified pharmacies no later than 90 calendar days after they have placed the first order for ZULRESSO and annually thereafter of healthcare settings and pharmacies that have ordered ZULRESSO, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
25. Audit all wholesalers-distributors no later than 90 calendar days after they become authorized to distribute the drug and annually thereafter, to ensure that all REMS processes and procedures are in place, functioning, and support the REMS Program requirements.
26. Take reasonable steps to improve implementation of and compliance with the requirements in the ZULRESSO REMS Program based on monitoring and evaluation of the ZULRESSO REMS Program.

## **IV. REMS Assessment Timetable**

Sage Therapeutics, Inc. must submit REMS assessments at 6 months, 12 months and annually thereafter from the date of the initial approval of the REMS (03/19/2019). 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. Sage 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 ZULRESSO REMS:

### **Enrollment Forms**

Healthcare Setting:

1. [Healthcare Setting Enrollment Form](#)

Patient:

2. [Patient Enrollment Form](#)

Pharmacy:

3. [Pharmacy Enrollment Form](#)

### **Training and Educational Materials**

Healthcare Setting:

4. [Training for Healthcare Settings](#)
5. [Healthcare Setting Knowledge Assessment](#)

Patient:

6. [Patient Information Guide](#)

Pharmacy:

7. [Program Overview](#)

### **Patient Care Form**

8. [Post Infusion Form](#)
9. [Excessive Sedation and Loss of Consciousness Adverse Event Form](#)

### **Communication Materials**

10. [Letter for Healthcare Providers](#)

## Other Materials

11. [REMS Program Website](#)