

Table of Contents

- **Training for Healthcare Settings** 3–16
- **Ordering Instructions** 17–18
- **Resources** 19–20

Training for Healthcare Settings

What Is ZULRESSO™ (brexanolone) injection?

- ZULRESSO is indicated for the treatment of postpartum depression (PPD) in adults.
- Pregnancy: Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm.
- ZULRESSO is intended for dilution and administration as a continuous intravenous infusion.
- ZULRESSO is available only through the ZULRESSO REMS.

ZULRESSO Has a Boxed Warning

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

- **Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO.**
- **Because of the risk of serious harm, patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Patients must be accompanied during interactions with their child(ren).**
- **ZULRESSO is available only through a restricted program called the ZULRESSO REMS.**

What Was Observed in the ZULRESSO Clinical Program?

- In premarketing clinical studies, the following observations were noted:
 - ZULRESSO caused sedation and somnolence that required in some patients with PPD dose interruption or reduction during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients).
 - Some patients with PPD were also reported to have loss of consciousness or altered state of consciousness during the ZULRESSO infusion (4% of the ZULRESSO-treated patients compared with 0% of the placebo-treated patients).
 - All patients with loss of or altered state of consciousness recovered with dose interruption; time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes.
 - Three ZULRESSO-treated patients who had a dosage interruption because of loss of consciousness subsequently resumed and completed treatment after resolution of symptoms; two patients who had dosage interruption because of loss of consciousness did not resume the infusion.
 - There was no clear association between loss or alteration of consciousness and pattern or timing of dose. Not all patients who experienced a loss or alteration of consciousness reported sedation or somnolence before the episode.
 - A healthy 55-year-old man participating in a cardiac repolarization study experienced severe somnolence and <1 minute of apnea while receiving two times the maximum recommended dosage of ZULRESSO (180 mcg/kg/hour).
- There is limited clinical trial experience regarding human overdosage with ZULRESSO. In premarketing clinical studies, two cases of accidental overdosage due to infusion pump malfunction resulted in transient loss of consciousness. Both patients regained consciousness approximately 15 minutes after discontinuation of the infusion without supportive measures. After full resolution of symptoms, both patients subsequently resumed and completed treatment. Overdosage may result in excessive sedation, including loss of consciousness and the potential for accompanying respiratory changes.
- These are not all of the adverse events observed in these trials.*

***Please see Prescribing Information, including Boxed Warning and Medication Guide.**

What Is the ZULRESSO REMS?

- The ZULRESSO Risk Evaluation and Mitigation Strategy (REMS) is a safety program to manage the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the ZULRESSO infusion.
- A REMS is required by the Food and Drug Administration (FDA) to ensure the potential benefits of a treatment outweigh its risks.

ZULRESSO REMS Overview:

- Administration of ZULRESSO to patients only in a medically supervised Healthcare Setting that provides monitoring while ZULRESSO is being administered.
- Only certified Pharmacies and Healthcare Settings can dispense ZULRESSO.
- Educate patients on the risk of serious harm from excessive sedation and sudden loss of consciousness and the need for monitoring while ZULRESSO is administered.
- Enroll all patients in a registry to characterize these risks and support safe use.

How to Become a Certified Healthcare Setting

STEP 1: Designate and Maintain an Authorized Representative. The Authorized Representative will carry out the certification process and oversee implementation and compliance with the ZULRESSO REMS on behalf of the Healthcare Setting.

- An Authorized Representative is a responsible individual assigned by the Healthcare Setting and its associated clinic(s).
- Each Healthcare Setting must designate one Authorized Representative who enrolls in the ZULRESSO REMS on behalf of the Healthcare Setting and attests to comply with the REMS requirements included in the Healthcare Setting Enrollment Form.
- A Healthcare Setting must be recertified in the ZULRESSO REMS if a new Authorized Representative is designated.

How to Become a Certified Healthcare Setting (continued)

The Authorized Representative will complete the following steps:

STEP 2: Review this Training and the Prescribing Information.

STEP 3: Complete the Healthcare Setting Knowledge Assessment. All questions in the Healthcare Setting Knowledge Assessment must be answered correctly to become certified.

STEP 4: Complete the Healthcare Setting Enrollment Form.

STEP 5: Submit the completed Healthcare Setting Knowledge Assessment and the Healthcare Setting Enrollment Form.

STEP 6: Implement the necessary processes and procedures to administer the ZULRESSO REMS.
The ZULRESSO REMS will notify the Authorized Representative of successful certification within 2 business days.

Healthcare Setting Requirements

- A healthcare provider must be available continuously on-site to oversee each patient for the duration of the infusion, and trained on the requirements of the ZULRESSO REMS. As a continuous intravenous (IV) infusion, treatment lasts a total of 60 hours (2.5 days).
- The facility must have a fall precautions protocol in place and be equipped with a programmable peristaltic IV infusion pump with alarm and continuous pulse oximetry with an alarm.
- Staff at the Healthcare Setting must be trained on the processes and procedures to administer ZULRESSO.

The Healthcare Setting must comply with audits by Sage Therapeutics, Inc., the FDA, or a third party acting on behalf of Sage Therapeutics, Inc. to ensure that all training, processes, and procedures are in place and are in compliance with the ZULRESSO REMS. The Authorized Representative of the Healthcare Setting must maintain documentation that all ZULRESSO REMS–required processes and procedures are in place and are being followed.

Before Administering ZULRESSO

Counsel the patients using the Patient Information Guide and provide a copy to the patient.

Enroll the patient in the ZULRESSO REMS by providing the Patient Enrollment Form and ask the patient to **complete** and **sign** the form. The ZULRESSO REMS trained healthcare provider assisting the patient with enrollment must also sign the Patient Enrollment Form and include their name and title. Retain a copy of the completed form in the patient's record.

Submit the completed Patient Enrollment Form.

Patient Counseling

Patients need to know that:

- They may experience excessive sedation or loss of consciousness during the ZULRESSO infusion, which could cause serious harm.
- They must alert a healthcare provider during the infusion if they have any symptoms associated with excessive sedation, such as:
 - Feeling extremely sleepy and being unable to stay awake when not planning to sleep
 - Impaired alertness and attention
 - Difficulty following simple instructions
 - Feeling lightheaded, dizzy, or like they are going to pass out
- They must enroll in the ZULRESSO REMS in order to receive ZULRESSO.
- They will be continuously monitored by pulse oximetry during the infusion.
- A healthcare provider will oversee the ZULRESSO infusion.
- They **cannot** be the primary caregiver for their child(ren) during the infusion. They must be accompanied during interactions with their child(ren) while receiving the infusion because of the risk of serious harm from excessive sedation and sudden loss of consciousness.
- Taking certain other medications or alcohol together with ZULRESSO can make these side effects more likely to occur.
- They should not engage in potentially hazardous activities requiring mental alertness, such as driving, after the infusion until any sedative effects of ZULRESSO have dissipated.

During the Administration of ZULRESSO

The infusion must be administered using an intravenous programmable infusion pump with alarms to alert if the pump malfunctions and started early enough during the day in order to monitor for excessive sedation.

Patient Monitoring:

- A healthcare provider must monitor the patient every 2 hours during the ZULRESSO infusion during planned, non-sleep periods.
- Patients must be continuously monitored for hypoxia by pulse oximetry with an alarm during the infusion.
- Immediately stop the infusion if pulse oximetry indicates hypoxia. If hypoxia occurs the infusion should not be restarted.
- Immediately stop the infusion if there are signs or symptoms of excessive sedation. After symptoms resolve, the infusion may be resumed at the same or lower dose as clinically appropriate.
- Staff at the Healthcare Setting should report all adverse events by contacting Sage Therapeutics, Inc. at 844-472-4379 or FDA at www.fda.gov/medwatch or call 800-FDA-1088.

After the Administration of ZULRESSO

After treatment discontinuation, and prior to discharge:

- Assess the patient's level of sedation.

Submit the Post Infusion Form:

- The Post Infusion Form must be submitted to the ZULRESSO REMS after the completion of the infusion, if the patient receives any part of the infusion, or if the infusion has been cancelled. If the infusion has been rescheduled, the form should be completed at that time.
- Submit the Post Infusion Form to the ZULRESSO REMS within 3 business days from the date of the patient completing the infusion or the scheduled infusion completion date.
- The Post Infusion Form is available at the ZULRESSO REMS website (www.zulressorems.com).

How to Report an Event of Excessive Sedation or Loss of Consciousness

Reporting Procedures:

If a patient experiences an event of excessive sedation or loss of consciousness:

- 1) Indicate the event on the **Post Infusion Form**.
 - 2) Complete the **Excessive Sedation and Loss of Consciousness Adverse Event Form**.
 - 3) Submit both forms to the ZULRESSO REMS.
- The Post Infusion Form and Excessive Sedation and Loss of Consciousness Adverse Event Form are available at www.zulressorems.com.
 - You may be contacted for further information on reported events by the Sage Therapeutics, Inc. Drug Safety Department.
 - For the purposes of this REMS and event reporting, the events are further characterized below:
 - Excessive sedation: impaired alertness and attention or difficulty following simple instructions, which precludes the patient from completing daily tasks. Patient is frequently drowsy and may fall asleep during activities (e.g., conversation, eating).
 - Loss of consciousness: total loss of awareness of the patient's self and surroundings manifest by lack of responsiveness to loud or noxious stimuli. Patient is not rousable to loud voice or with firm physical contact, including shaking. This is in contrast to sleep which is physiologic and intrinsically reversible with sufficient stimuli.

To report any SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 844-472-4379 or FDA at 800-FDA-1088 or www.fda.gov/medwatch.

REMS Requirements Specific for Pharmacies within the Certified Healthcare Setting

Pharmacies within the certified Healthcare Setting must:

- Maintain records of all prepared and dispensed ZULRESSO.
- Maintain records documenting that all ZULRESSO REMS-required processes and procedures are in place and being followed, including records of staff training.
- Not distribute, transfer, loan, or sell ZULRESSO.
- 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.

Any Pharmacy not part of the certified Healthcare Setting must be certified before they can dispense ZULRESSO. For more information, see Program Overview for Pharmacies.

Ordering Instructions

How to Order Product

To order vials of ZULRESSO:

- Contact the ZULRESSO REMS at **844-472-4379** for a current list of enrolled distributors.

To order ZULRESSO prepared for administration:

- If product will be prepared within the certified Healthcare Setting, follow the protocol and procedures established by the Authorized Representative.
- If product will be prepared outside the Healthcare Setting, contact an enrolled Pharmacy to place an order for ZULRESSO. Contact the ZULRESSO REMS at **844-472-4379** for a current list of enrolled Pharmacies.

Resources

ZULRESSO REMS Resources

For more information about the ZULRESSO REMS, visit www.zulressoems.com or call the ZULRESSO REMS at 844-472-4379. The resources below are available for download at www.zulressoems.com.

Healthcare Settings

- ZULRESSO Prescribing Information
- ZULRESSO Medication Guide
- ZULRESSO REMS Training
- ZULRESSO REMS Healthcare Setting Enrollment Form
- ZULRESSO REMS Healthcare Setting Knowledge Assessment
- ZULRESSO REMS Patient Enrollment Form
- ZULRESSO REMS Post Infusion Form
- ZULRESSO REMS Patient Information Guide
- Excessive Sedation and Loss of Consciousness Adverse Event Form

Patients

- ZULRESSO REMS Patient Information Guide
- ZULRESSO Medication Guide
- ZULRESSO REMS Patient Enrollment Form

Pharmacies

- ZULRESSO Prescribing Information
- ZULRESSO Medication Guide
- Program Overview for Pharmacies

