

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**211371Orig1s000**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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| <b>Application Type</b>       | NDA   |
| <b>Application Number</b>     | 211371  |
| <b>PDUFA Goal Date</b>        | March 19, 2018  |
| <b>OSE RCM #</b>              | 2018-851  |
| <b>Reviewer Name(s)</b>       | Leah M Hart, Pharm.D.<br>Kate Oswell<br>Carolyn Tieu, Pharm.D., MPH   |
| <b>Team Leader</b>            | Selena Ready, Pharm.D.  |
| <b>Division Director</b>      | Cynthia LaCivita, Pharm.D.  |
| <b>Review Completion Date</b> | March 19, 2019  |
| <b>Subject</b>                | Evaluation of Need for a REMS   |
| <b>Established Name</b>       | brexanolone   |
| <b>Trade Name</b>             | Zulresso  |
| <b>Name of Applicant</b>      | Sage Therapeutics   |
| <b>Therapeutic Class</b>      | Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator  |
| <b>Formulation(s)</b>         | Injection: 10 mg/20 mL (5 mg/ mL) single-dose vial, dilution is required prior to administration.   |
| <b>Dosing Regimen</b>         | Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows: <ul style="list-style-type: none"><li>• 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour</li><li>• 4 to 24 hours: Increase dosage to 60 mcg/kg/hour</li><li>• 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (alternatively consider a dosage of 60 mcg/kg/hour for those who do not tolerate 90 mcg/kg/hour)</li><li>• 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour</li><li>• 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour</li></ul> |

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## **EXECUTIVE SUMMARY**

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Zulresso (brexanolone) is necessary to ensure the benefits outweigh its risks. Sage Therapeutics submitted a New Drug Application (NDA) 211371 for Zulresso with the proposed indication for the treatment of postpartum depression. Zulresso is available as a 5 mg/ mL solution, which is administered as an intravenous infusion over 60 hours. The risks associated with Zulresso include excessive sedation and sudden loss of consciousness and are the focus of this review. The applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

If approved, Zulresso will provide a treatment option for women with post-partum depression for which there is an unmet need. Due to the risk of serious harm resulting from excessive sedation and sudden loss of consciousness, risk mitigation measures beyond the approved labeling are necessary. DRISK and the Division of Psychiatric Products (DPP) have determined that a REMS with ETASU is required to ensure the benefits of Zulresso outweigh the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the ZULRESSO infusion. A REMS with ETASU will ensure that: 1) Zulresso is administered only to patients in a medically supervised setting that provides monitoring for the duration of the infusion and 2) each patient is enrolled in a registry, informed of the adverse events of excessive sedation and loss of consciousness and, the need for monitoring.

The Applicant's amended REMS submission received on March 15 and 18, 2019 has included all the necessary changes communicated on January 18, February 1, March 7, March 14, and March 18, 2019. DRISK is recommending approval of the Zulresso REMS.

## **1 Introduction**

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This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) brexanolone (Zulresso) is necessary to ensure the benefits outweigh its risks. Sage Therapeutics, Inc. (Applicant) submitted a New Drug Application (NDA) 211371 for Zulresso with the proposed indication for the treatment of postpartum depression (PPD) in adults. This application is under review in the Division of Psychiatric Products (DPP). The Applicant's proposed REMS submitted on November 8, 2018 consisted of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The goal of the REMS was to mitigate the risk of negative comes resulting from loss of consciousness (LOC). DRISK and DPP agree that a REMS with ETASU is necessary but our proposed REMS differed from the Applicant initial proposal regarding the risks that are covered by the REMS and the elements. Based on review of the application, feedback from the REMS Oversight Committee (ROC) and feedback from the joint meeting of the Psychopharmacologic Drugs Advisory Committee (PDAC) and Drug Safety and Risk Management (DSaRM) Advisory Committee, DRISK is recommending that a REMS with ETASU B (pharmacy and healthcare setting certification), C (administration only in a certified healthcare setting), D (safe use conditions), E (patients are subject

to certain monitoring), and F (each patient is enrolled in a registry) is necessary for the benefits of Zulresso to outweigh the potential risk of serious harm resulting from excessive sedation and sudden LOC. Submissions on March 15 (Seq No 0031) and March 18, 2019 (Seq No 0032 & 0033) constitute a complete REMS proposal and are the subject of this review.

### 1.1 DRISK REVIEWS CONTRIBUTING TO THIS ORIGINAL APPLICATION

- Hart, L. Division of Risk Management Review of the Zulresso REMS materials and Supporting Document, submitted to DARRTS January 18, 2019.
- Hart, L. Division of Risk Management Review of the Zulresso REMS materials and Supporting Document, submitted to DARRTS February 1, 2019.
- Hart, L. Division of Risk Management Review of the Zulresso REMS materials and Supporting Document, submitted to DARRTS March 7, 2019.
- Hart, L. Division of Risk Management Review of the Zulresso REMS materials and Supporting Document, submitted to DARRTS March 14, 2019.

## 2 Background

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### 2.1 PRODUCT INFORMATION

Zulresso, a new molecular entity<sup>a</sup>, is an allosteric modulator of GABA<sub>A</sub> receptors and chemically identical to the endogenous metabolite of progesterone, allopregnanolone, proposed for the treatment of PPD. If approved, Zulresso would be the first in class.

Zulresso is available as a 5 mg/ mL injection, which is diluted and administered as a continuous intravenous infusion over 60 hours.<sup>b</sup> Once mixed, the infusion is stable for 12 hours at room temperature and 24 hours with refrigeration. The recommended dose is weight-based and time-based as follows:

- 0 to 4 hours at 30 µg/kg/hour
- 4 to 24 hours at 60 µg/kg/hour
- 24 to 52 hours at 90 µg/kg/hour
- 52 to 56 hours at 60 µg/kg/hour
- 56 to 60 hours at 30 µg/kg/hour

The intended setting in which the drug will be administered is a medically supervised setting capable of clinically monitoring the patient over the duration of the infusion and intervening if the patient experiences excessive sedation or sudden LOC. Zulresso is not currently approved in any jurisdiction.

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<sup>a</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

<sup>b</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

Given that there are no currently approved treatments for PPD in the US, Zulresso was granted priority review.

## 2.2 REGULATORY HISTORY

The following is a summary of the regulatory history and pertinent internal meetings for NDA 211371 relevant to this review:

- 08/23/2016: Breakthrough Therapy designation granted.
- 04/19/2018: NDA 211371 submission for the treatment of post-partum depression received. The Applicant did not submit a REMS proposal.
- 07/26/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency communicated the concern that unpredictable, abrupt loss of consciousness requiring intervention (turning off the infusion) could represent a danger to the patient or the patient's infant if not continuously monitored. Coupled with the need for dose adjustments (every 4 hours during the taper phase), the Agency stated that an inpatient setting may be required to ensure the safe use of this product. The Applicant proposed that there may be appropriate non-hospital settings for administration of this product. They suggested infusion centers and rehab facilities, among others. The Agency stated that we would need additional details to evaluate any such proposal and that, regardless of setting ultimately selected, the capacity for 24-hour monitoring and availability of medical or nursing staff are critical features. The Applicant believes there may be ways for this product to be administered safely at home. Based on the current data, the Agency disagreed and communicated that the REMS would be discussed at the AC. The Agency stated that, for home administration to be feasible, identifying patients at risk for adverse events in advance is crucial. The Applicant indicated that they would be willing to explore this. The Agency informed the Applicant that based on the currently available data, a REMS with ETASU would likely be necessary for Zulresso.
- 10/03/18: REMS Oversight Committee meeting. The ROC agreed that a REMS with ETASU is necessary for the benefits of Zulresso to outweigh the risk of LOC and the required elements are administration only in a certified healthcare setting capable of continuous monitoring and a patient registry.
- 10/09/2018: Medical Product Policy Regulatory Council meeting held to discuss the unique administration of Zulresso. The Council agreed that a REMS is necessary to ensure the benefits outweigh the risk.
- 10/22/2018: Late Cycle Meeting with Applicant. The Agency communicated that a REMS with ETASU including a registry to further characterize the risk was required for the benefits of Zulresso to outweigh the risk and Sage agreed. The Applicant and the Agency discussed the dilution/administration proposal of Zulresso. The Applicant's proposal was to have

(b) (4)

The Agency recommended *a standard concentration* (where dose would be based on infusion rate). Also, during the meeting, the Applicant and Agency discussed exploring alternative administration schedules that might increase access to brexanolone such as an interrupted brexanolone infusion in which Zulresso is given only during the daytime (allowing the patient to go home at night and administration at non-24-hour facilities). The Applicant and Agency briefly reviewed whether the Applicant was considering developing a potential REMS program for home infusion to be discussed at the AC. The Applicant and the Agency determined that at the present time, a proposed REMS designed for home infusion was not an option.

- 11/01/2018: Amendment containing a REMS Document received (Seq No. 024).
- 11/02/2018: Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Meeting was convened to discuss Zulresso. The Committee unanimously agreed (18/0) that substantial evidence was presented by the Applicant to support a claim of effectiveness for brexanolone for the treatment of PPD. Most committee members agreed that the Applicant adequately characterized the safety profile of brexanolone for the treatment of PPD. These members agreed that the excessive sedation and loss-of-consciousness events can be addressed through a REMS, and the AC voted 17/1 in favor of the benefits outweighing the risks with a REMS in place. Some members mentioned that the use of the drug should be restricted to the inpatient hospital settings. However, other members noted that the Agency should not dictate setting because it would be too restrictive and stifle innovation of clinics/providers to meet the recommended safety parameters outlined in the REMS for safe administration of the drug. Members agreed that the frequency of sedation monitoring should be outlined in the REMS. The panel members recommended the use/development of a structured sedation scale to monitor loss-of-consciousness. They recommended certification of all staff who would administer and monitor the infusion of the drug. Also advised that developing standardized order sets may reduce medication errors. The members recommended the clinical setting should have provisions for pulse oximetry and/or respiration monitoring and cardiopulmonary resuscitation (CPR availability). They also advised that the REMS should include that patients must be accompanied during all interactions with their children for the entire time of the infusion. Members also favored the Agency working with the Applicant to simplify the infusion paradigm (b) (4) and that the product be prepared in a pharmacy under sterile conditions. They also mentioned that the REMS should caution against co-administration of brexanolone with GABAergic drugs (benzodiazepines, barbiturates, anti-convulsant) and

opioid drugs (methadone, buprenorphine) that may increase risk for sedation related adverse events. (Refer to the full transcript for details of the committee discussion.)<sup>c</sup>

- 11/08/2018: Amendment containing a complete REMS submission (REMS document, supporting document and appended materials) was received (Seq No 025). The Applicant proposed the following goal for the Zulresso REMS Program:

*The goal of the Zulresso REMS Program is to mitigate the risk of negative outcomes resulting from the loss of consciousness during the infusion by ensuring:*

 (b) (4)

- 11/15/2018: Major amendment acknowledgment letter sent to the applicant; PDUFA goal date extended by 3 months

 (b) (4)

- 01/18/2019: Preliminary comments based on review of the REMS and appended materials were sent to the Applicant consistent with DRISK review.
- 01/24/2019: Telephone conference with the Applicant to discuss the REMS structure and timing for amendment.
- 02/01/2019: Information Request (IR) letter sent to the Applicant with the REMS document and attestations
- 02/15/2019: Applicant submitted an amendment containing a complete REMS submission with edits consistent with DRISK review (Seq No 028)
- 03/07/2019: Comments sent to Applicant based on review of the REMS and appended materials consistent with DRISK review
- 03/11/2019: Applicant submitted an amendment containing a complete REMS submission with edits consistent with DRISK review (Seq No 029)
- 03/14/2019: Comments sent to Applicant based on review of the REMS and appended materials consistent with DRISK review

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<sup>c</sup> Transcript for the November 2, 2018, Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Psychiatry Drug Products Advisory Committee (PAC):

- 03/15/2019: Applicant submitted an amendment containing a complete REMS submission with edits consistent with DRISK review (Seq No 031)
- 03/17/2019: Comments sent via email to Applicant based on review of the REMS and appended materials consistent with DRISK review
- 03/18/2019: Comments sent via email to the Applicant based on review of the REMS and appended materials; the Applicant submitted a REMS document, REMS Supporting Document, Healthcare Setting Enrollment Form, Healthcare Setting Knowledge Assessment, Letter for Healthcare Providers, Post Infusion Form, and Program Overview for Pharmacies (Seq No 032 and 033)

### **3 Therapeutic Context and Treatment Options**

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#### **3.1 DESCRIPTION OF THE MEDICAL CONDITION**

Post- or peripartum depression is a major depressive episode with onset during pregnancy or the first 4 weeks after birth. The estimated incidence rate of PPD in the United States is 12% of births.<sup>1</sup> PPD symptoms can include but aren't limited to depressed mood, anhedonia, significant weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness or excessive guilt, and diminished ability to think or concentrate.<sup>2</sup>

The effects of post-partum depression impact the entire family unit. The most common cause of maternal death after childbirth in the developed world is suicide.<sup>3,d</sup> PPD can have a detrimental impact on the mother-infant relationship and places the infant at an increased risk of impaired mental and motor development, difficult temperament, poor self-regulation, low self-esteem, and behavior problems.<sup>4</sup>

Given the incident rate and the estimated 4 million births annually the population likely to use this drug could be 480,000 patients per year.<sup>e</sup>

#### **3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS**

There are currently no FDA approved treatments for PPD. Non-approved treatments include selective-serotonin reuptake inhibitors (SSRI) and selective- serotonin norepinephrine inhibitors (SSNRI). These pharmacological options may take 4-6 weeks to take effect and there is little evidence of their efficacy in PPD.

Non-pharmacologic treatment options include a multitude of psychotherapeutic treatments (i.e. cognitive-behavioral therapy, and interpersonal psychotherapy).

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<sup>d</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

<sup>e</sup> Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

## 4 Benefit Assessment

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The efficacy and safety of brexanolone for the treatment of post-partum depression was determined based on three pivotal studies- one phase-2 study (202A) and two phase-3 studies (202B and 202C). The three studies were similar in design: randomized, double-blind, and placebo-controlled. Each of these studies had the same primary efficacy endpoint: change in baseline on the Hamilton Depression Rating Scale (HAM-D) at 60 hours after the start of the brexanolone infusion. Women with bipolar disorder, active psychosis, or a suicide attempt during index episode were excluded from the studies.

Study 202 A was a Phase 2 study comparing brexanolone 90 mcg/kg/h (n=10) to placebo (n=11) in patients with severe PPD (HAM-D>26). Brexanolone was significantly superior to placebo (p=0.008).

Study 202 B was a Phase 3 study comparing brexanolone 90 mcg/kg/h (n=45) and brexanolone 60 mcg/kg/h (n=47) to placebo (n=46) in patients with severe PPD (HAM-D > 26). Brexanolone 60 mcg/kg/h and 90 mcg/kg/h were significantly superior to placebo (p=0.0013 and 0.0252 respectively).

Study 202 C was a Phase 3 study comparing brexanolone 90 mcg/kg/h (n=54) to placebo (n=54) in patients with moderate PPD (HAM-D 20 to 25). Brexanolone was significantly superior to placebo (p=0.0160).

In addition, pooled dosing arms at Day 30 showed that patients treated with brexanolone 90 mcg/kg/h and 60 mcg/kg/h were still superior to placebo-treated patients. The clinical reviewer concluded that the three studies submitted by the Applicant meet the evidentiary standard for the demonstration of brexanolone's effectiveness for the treatment of postpartum depression. The studies demonstrate a clinically meaningful effect because the improvement in depressive symptoms is both consistent with the effects of other antidepressants and occurs much quicker than other available treatments (after 60 hours versus 4 weeks).<sup>f,g</sup>

## 5 Risk Assessment & Safe-Use Conditions

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The safety database is comprised of 140 patients with PPD exposed to brexanolone. In clinical trials, sedation and somnolence associated adverse events (AEs) were the most common reported AEs (15% of brexanolone patients compared to 6% in placebo). This was followed by dizziness, lightheadedness, presyncope, vertigo (12% of brexanolone patients compared to 7% for placebo treated patients). Loss of consciousness, or syncope was reported in 6 patients in the brexanolone-treated patients and none in the placebo patients.

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<sup>f</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

<sup>g</sup> Fisher, Bernard. FDA Clinical Review of NDA 211371. March 19, 2019.

There were two serious adverse events (SAEs) in this program. One subject reported suicidal ideation and intentional overdose, however the patient's emergency department evaluation was inconsistent with a suicide attempt and she was not admitted. Once subject will further be discussed in section 5.1 below had syncope/altered state of consciousness. There were no deaths in the clinical development program.

## **5.1 POTENTIAL RISK OF SERIOUS HARM**

Excessive sedation and sudden LOC during the infusion was the identified risk in the brexanolone development program.

The Agency is concerned that patients may experience serious adverse outcomes because of the excessive sedation and LOC seen in the clinical development program. Some of these potential risks of serious harm could include falling, accidental drowning, or harm to dependents if the patient were to lose consciousness unwitnessed and with no intervention. In the clinical development program, all patients were monitored continuously by study personnel for the duration of the infusion. As discussed above, sedation was observed in the treatment population as well as incidences of LOC. In clinical trials of brexanolone, 6 out of 140 (4%) patients experienced a loss of consciousness, syncope, or presyncope. One patient appeared to have a vasovagal reaction to a blood draw and one reported dizziness and vertigo that improved when she sat down. The other four patients seemed to experience an abrupt onset of deep sleep- characterized as a loss of consciousness. All LOC events resolved within 15 to 60 minutes of the infusion discontinuation and required no further intervention other than infusion interruption. Two patients have a reported pump malfunction, although blood levels do not indicate abnormally high doses.

One patient experienced an LOC related serious adverse events 8.5 hours after the start of the infusion. She experienced dizziness, then became unresponsive. Her infusion was stopped 3 minutes after she became unresponsive and after 10 minutes she opened her eyes to verbal stimuli but was not verbally responsive. She became verbally responsive after an additional 45 minutes and was transferred to the local emergency room for further work up. Her exam and labs were unremarkable and was amnestic for events from her LOC until she was in the emergency room.

To answer the Agency's concern about the correlation between Zulresso's fairly long half-life and LOC, the Applicant presented a graph, at the Late-cycle meeting, showing that most Zulresso was cleared from peripheral circulation in 40 minutes. The Agency suggested that peripheral concentrations may not reflect Central Nervous System (CNS) concentrations. However, the Applicant stated that they have non-clinical data from a previous development program that show the concentrations are similar. The Agency acknowledged that, during loss-of-consciousness events, patients recovered minutes after stopping the infusion.

The clinical reviewer has concluded that there is no discernable pattern to the LOC events and at this time there are no predictors of these events. Dosing, time on brexanolone, blood levels, BMI, past medical history and concurrent medications all varied.<sup>h</sup>

In addition, one subject in the cardiac repolarization study also lost consciousness. This was a 55-year old man with no reported past medical history who developed somnolence, confusion and dizziness while receiving 150mcg/kg and experienced less than 1 minute of apnea during the event.

## 6 Expected Postmarket Use

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Zulresso is likely to be prescribed by specialists, psychiatry and obstetrics-gynecology, as well as general practitioners who treat depression. Given the need to continuously monitor patients to ensure safe administration of Zulresso, it is likely that Zulresso will be administered in a hospital. For this product, hospitals would be capable of providing all aspects of the medication use process including; diagnosis, prescribing, dispensing, administering and monitoring.

A variety of outpatient study centers were utilized during the clinical development program as a site to provide the 60-hour infusion. These included clinical research units (on and off hospital campuses), sleep centers, Phase 1 units (units used in the Phase 1 clinical development program), day surgery centers, an urgent care facility, a specialty maternal health psychiatric unit, and a physician outpatient office.

Although Zulresso was not studied or evaluated for home administration, the Applicant initially proposed home administration as a site for administration. They [Applicant] had conveyed that “the proposed labeling for brexanolone is purposely silent on the site of administration because a variety of infusion settings are envisioned. The labeling includes a variety of instructions, precautions and warnings that we believe provide for safe use in a variety of settings with well-established infrastructure, including outpatient settings (e.g., home infusion, outpatient infusion centers).”

## 7 Risk Management Activities Proposed by the Applicant

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The Applicant has proposed risk management activities for Zulresso beyond routine pharmacovigilance and labeling including a REMS with ETASU to mitigate the risk of serious harm resulting from excessive sedation and sudden LOC.

### 7.1 REVIEW OF APPLICANT’S PROPOSED REMS

The Applicant submitted a proposed REMS document on November 1, 2018 and subsequently a complete REMS proposal including a REMS document, supporting document and appended

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<sup>h</sup> Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

materials on November 8, 2018 as an amendment to their original NDA submission dated April 19, 2018. The initial REMS document received on November 1, 2018 proposed use of Zulresso as a home infusion. The submission received on November 8, 2018 included the proposed REMS document, (b) (4) healthcare setting certification, a patient registry, implementation system, and a timetable for submission of assessments. These strategies included educating all stakeholders involved with the prescribing, dispensing and administration of the drug including monitoring by a healthcare provider for the duration of the infusion. After further discussions, amendments and ultimately alignment with the Agency (see section 2.2, regulatory history), the Applicant amended their proposed REMS and provided components that constitute a final submission on March 15 and 18, 2019, which is the subject of this review. The proposed REMS as amended includes ETASU B (pharmacy and healthcare setting certification), ETASU C (the drug only dispensed in certified healthcare setting), ETASU D (safe use condition), ETASU E (patient monitoring), ETASU F (patient registry), an implementation system and a timetable for submission of assessments.

**Reviewer Comments:** *The REMS is necessary to ensure the benefits of Zulresso outweigh the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the infusion. Administering Zulresso only in a healthcare setting capable of monitoring patients for excessive sedation or sudden loss of consciousness, with healthcare providers capable of interrupting the infusion if necessary, will mitigate the risk of harm to the patient. Patients will be enrolled in a registry and the information collected will be used to better characterize the risks and support safe use.*

### 7.1.1 REMS Goals

In the proposed REMS submitted on November 8, the Applicant proposed the following goal for the Zulresso REMS Program:

The goal of the Zulresso REMS Program is to mitigate the risk of negative outcomes resulting from the loss of consciousness during the infusion by ensuring:



On March 15 and 18, 2019, the Applicant amended their goal based on comments and discussions with the Agency to the following:

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.

**Reviewer Comments:** *Serious harm resulting from excessive sedation and sudden loss of consciousness are the most concerning risks with Zulresso, as patients may be at risk for accidents during the infusion if they are not monitored for these symptoms. The goal represents the main safety concerns with Zulresso and is acceptable.*

### **7.1.2 Elements to Assure Safe Use**

On March 15 and 18, 2019, the Applicant amended their REMS based on comments and discussions with the Agency.

#### **7.1.2.1 ETASU: (C) the drug can only be dispensed to patients in certain healthcare settings**

Healthcare setting certified in the REMS are required to counsel patients and enroll each patient in the REMS registry prior to administering Zulresso. Certified healthcare settings are required to monitor patients for the duration of the Zulresso infusion for excessive sedation and LOC and assess the patient's oxygen saturation using continuous pulse oximetry. Certified healthcare settings are also required to complete the Post Infusion Form and Excessive Sedation and Loss of Consciousness Adverse Event Form.

#### **7.1.2.2 ETASU: (B) pharmacy and healthcare setting that dispense the drug are specially certified**

Dispensing from a certified pharmacy supports the monitoring requirements stated in the REMS by ensuring that Zulresso is dispensed only to certified healthcare settings.

#### **7.1.2.3 ETASU: (D) Each patient using the drug be subject to certain safe-use conditions**

ETASU D will ensure 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. In addition to counseling by the certified healthcare setting, the patient enrollment form will be the material used to inform patients of the risks, the need for monitoring and about the patient registry.

#### **7.1.2.4 ETASU: (E) Each patient using the drug be subject to certain monitoring**

ETASU E will ensure each patient is monitored for the duration of the infusion to prevent serious harm resulting from excessive sedation and sudden loss of consciousness.

#### **7.1.2.5 ETASU: (F) Each patient using the drug be enrolled in a registry**

Enrolling each patient in the registry will allow for the collection of additional data that could better inform us about the risk and/or risk management. Specifically, the registry will help to better

characterize the risk, identify any possible risk factors, or discernable patterns that may predict who is at risk for excessive sedation or LOC.

Information regarding the infusion will be captured using a Post Infusion Form. If an adverse event occurs, the healthcare setting will be required to complete the Excessive Sedation and Loss of Consciousness Adverse Event Form.

**Reviewer Comments:** *Based on review of the application by DPP and DRISK, along with feedback from the ROC and the joint meeting of the PDAC and DSaRM Advisory Committee, DRISK recommends that to ensure the benefits outweigh the risk of serious harm the REMS must include the following ETASU: (B) pharmacy and healthcare setting certification, (C) dispensing of Zolresso only in a certified healthcare setting, (D) patient subject to safe-use conditions, (E) patient subject to certain monitoring, and (F) patient enrollment in a registry. We agree with the Applicant's proposed ETASUs. (Section 8 below provides additional rationale.)*

### **7.1.3 Implementation System**

The Applicant has proposed to include an implementation system including maintenance of a database of enrolled prescribers, enrolled patients, certified healthcare settings and contracted distributors. The Applicant has also proposed a Zolresso REMS website and a Zolresso REMS Program support for participants, which includes a toll-free number for stakeholders to interface with the REMS program.

**Reviewer Comments:** *The Agency agrees that an implementation system is necessary for the REMS program as it contains ETASU B and D.*

### **7.1.4 Timetable for Submission of Assessments**

The Applicant proposes to submit assessments to the FDA at 6 months, 12 months and annually thereafter from the date of the initial approval of the REMS Program.

**Reviewer Comments:** *The proposed timetable for the submission of assessments is acceptable.*

### **7.1.5 REMS Materials**

We have reviewed the following REMS Program materials submitted by Sage Therapeutics, Inc.:

- Enrollment Forms
  - Healthcare Setting Enrollment Form
  - Patient Enrollment Form
  - Pharmacy Enrollment Form
- Training and Educational Materials
  - Training for Healthcare Settings
  - Healthcare Setting Knowledge Assessment
  - Patient Information Guide
  - Program Overview
- Patient Care Form
  - Post Infusion Form

- Excessive Sedation and Loss of Consciousness Adverse Event Form
- Communication Material
  - Letter for Healthcare Providers
- Other Material
  - REMS Program Website

**Reviewer Comments:** *Initially, the Applicant did not include the following REMS materials: Pharmacy Enrolment Form, Program Overview, an Excessive Sedation and Loss of Consciousness Adverse Event Form, and a Patient Information Guide. The Agency informed the Applicant that these materials were necessary to support the REMS requirements. The Applicant included all the required materials in the March 15 and 18, 2019 submissions.*

*The Zulresso REMS training for healthcare settings can be used to train staff involved in the prescribing, dispensing, and administering of Zulresso. In addition, there will be content focused on healthcare providers who are responsible for monitoring the patient. This will provide details on how the patient should be monitored during the infusion and instructions on completing the Post Infusion Form and Excessive Sedation and Loss of Consciousness Adverse Event Form. Patient directed materials include the Patient Enrollment Form and a Patient Information Guide and are required to be provided to the patient. Finally, a REMS website will provide access to all materials online. The Applicant is proposing a modification in the future that would update the REMS website to include online enrollment capabilities.*

*These materials are acceptable to DRISK.*

#### **7.1.6 REMS Assessment Plan**

**Reviewer Comments:** *The REMS Assessment Plan as submitted on March 15 and 18, 2019 is acceptable.*

The REMS assessment plan must include, but is not limited to, the following:

1. REMS Program Implementation (6-month and 1-year assessments only)
  - a. Date of first commercial distribution of Zulresso
  - b. Date when the Zulresso REMS Website went live and was fully operational
  - c. Date when healthcare settings could become certified
  - d. Date when pharmacies could become certified
  - e. Date when patients could become enrolled
  - f. Date when REMS Call Center is established and fully operational
2. Program Outreach and Communication (6-month, 1-year, and 2-year assessments only)
  - a. Sources of the distribution lists for healthcare providers
  - b. Number of healthcare providers targeted
  - c. The date(s), number, and medical specialty of healthcare providers who were sent the Letter for Healthcare Providers by the methods of distribution

- d. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients
3. REMS Program Operation and Performance Data (per reporting period and cumulatively)
- a. REMS Website
    - i. Number of visits and unique visits to the REMS website
    - ii. Number of REMS materials downloaded or printed for each material
  - b. REMS Call Center
    - i. Number of contacts by stakeholder type (patients, healthcare providers, pharmacies, healthcare settings, wholesaler/distributors, other)
    - ii. Summary of reasons for calls (e.g., enrollment question, location of a certified healthcare setting) and by reporter (authorized representative, healthcare setting, patient/caregiver, other)
    - iii. Summary of frequently asked questions (FAQ) by stakeholder type
    - iv. Summary report of REMS-related problems identified and resulting corrective actions
4. REMS Enrollment Statistics (per reporting period and cumulatively)
- a. Healthcare Settings
    - i. Number of newly certified and active (i.e., that have received Zulresso) healthcare settings stratified by healthcare setting type (i.e. hospital, infusion center, other), authorized representative credentials, and geographic region
    - ii. Number of healthcare settings that dispensed Zulresso for administration stratified by healthcare setting type and geographic region
    - iii. Number of certified healthcare settings with an internal central pharmacy
    - iv. Number of certified healthcare settings without an internal central pharmacy
    - v. Healthcare settings that were unable to become certified and reason
  - b. Pharmacies
    - i. Number of newly enrolled and active (i.e., that have received Zulresso) pharmacies stratified by pharmacy type (i.e., specialty, specialty infusion, compounding, other), authorized representative credentials, and geographic region
    - ii. Number of pharmacies that dispensed Zulresso stratified by pharmacy type and geographic region
    - iii. Pharmacies that were unable to become certified and reason
  - c. Wholesalers/Distributors
    - i. Number of newly enrolled and active (i.e., that have shipped Zulresso) distributors
    - ii. Number of enrolled wholesalers/distributors that shipped Zulresso
  - d. Patients
    - i. Number of newly enrolled patients stratified by age, geographic region, and healthcare setting type

5. Zulresso Utilization Data (per reporting period and cumulatively)
  - a. Number of vials distributed to certified healthcare settings and certified pharmacies
  - b. Number of prescriptions dispensed to certified healthcare settings from certified pharmacies stratified by:
    - i. Pharmacy type
    - ii. Prescriber specialty, professional degree/credentials, geographic region
    - iii. Patient demographics (i.e., age and geographic region)
  - c. Number of unique patients receiving Zulresso, stratified by age, geographic region, and healthcare setting type
6. Post-Training Healthcare Setting Knowledge Assessments (per reporting period and cumulatively)
  - a. Number of completed post-training Healthcare Setting Knowledge Assessments, including number of attempts to complete per healthcare setting authorized representative and method of completion.
  - b. A summary of the most frequently missed Healthcare Setting Knowledge Assessment questions
  - c. A summary of potential comprehension or perception issues identified with the Knowledge Assessments
7. REMS Compliance (per reporting period and cumulatively)
  - a. Provide a summary of non-compliance identified, including but not limited to:
    - i. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each case, and which event lead to de-certification from the REMS.
    - ii. Provide a copy of the audit plan for each stakeholder
    - iii. Report of audit findings for each stakeholder (healthcare settings, pharmacies, wholesalers/distributors)
      1. The number of audits expected, and the number of audits performed.
      2. The number and types of deficiencies noted for each group of audited stakeholders.
      3. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit.
      4. For any that did not complete the CAPA within one month of the audit, describe actions taken.
      5. Include a unique ID for each stakeholder that had deviations to track deviations by stakeholder over time.
      6. Documentation of completion of training for relevant staff.
      7. The existence of documented processes and procedures for complying with the REMS
      8. Verification that each audited stakeholder's site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification.

- b. Healthcare settings (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
  - i. The number and type of healthcare settings for which non-compliance with the REMS is detected
  - ii. Number of times Zulresso was administered by a certified healthcare setting prior to patient enrollment
  - iii. Number and type of non-certified healthcare setting that administered Zulresso and the number of incidents for each healthcare setting.
  - iv. Number of healthcare settings that did not enroll patients prior to administering. Include the number of patients involved.
  - v. Number of times Zulresso was distributed, transferred, or loaned from one healthcare setting to another
  - vi. Number of healthcare settings that did not provide appropriate monitoring for the duration of the infusion. Include the number of patients involved and the proportion of patients per healthcare setting.
  - vii. Number of healthcare settings that did not have the necessary equipment (i.e. continuous pulse oximetry, fall precaution protocol, intravenous programmable infusion pumps with alarms). Include the number of patients involved.
  - viii. Number of patients who refused to comply with the duration of the infusion period. Include the number of healthcare settings involved and the proportion of patients per healthcare setting
  - ix. Number of patients who were not enrolled and received a Zulresso infusion in a certified healthcare setting
  - x. Number of healthcare settings de-certified for non-compliance and reasons for de-certification
  
- c. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
  - i. The number and type of pharmacies for which non-compliance with the REMS is detected
  - ii. The number and type of non-certified pharmacies that dispensed Zulresso and the number of incidents for each
  - iii. Number of times Zulresso was dispensed to healthcare setting without verifying that the healthcare setting is certified
  - iv. Number of pharmacies who were de-certified for non-compliance and reasons for de-certification.
  
- d. Wholesalers/Distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
  - i. The number of authorized wholesalers/distributors for which non-compliance with the REMS is detected
  - ii. The number and type of non-authorized wholesalers/distributors that shipped Zulresso and the number of incidents for each
  - iii. Number of times Zulresso was distributed to a non-certified healthcare setting, non-certified pharmacy, or directly to patients.
  
- e. Post Infusion Forms

- i. Number of Post Infusion Forms expected, received, and outstanding as of the report cut-off date
      - ii. Number of Post Infusion Forms not received within 3 calendar days. Include outreach activities performed to collect the forms.
      - iii. Number of Post-Infusion Forms not received within 15 calendar days. Include outreach activities performed to collect the forms.
      - iv. Number of Post Infusion Forms not received within 30 calendar days. Include outreach activities performed to collect the forms and corrective actions taken.
      - v. Number of Post Infusion Forms where a patient was enrolled but did not received Zulresso and reasons why this occurred.
      - vi. Results of Post-Infusion Forms outstanding from previous reporting periods (if applicable)
      - vii. Any other evidence that safe use was not demonstrated (patient was not monitored for sufficient period or appropriate monitoring was not done).
    - f. Excessive Sedation and Loss of Consciousness Adverse Event Forms
      - i. Number of Excessive Sedation and Loss of Consciousness Adverse Event Forms expected, received, and outstanding as of the report cut-off date
      - ii. Number of Excessive Sedation and Loss of Consciousness Adverse Event Forms not received within 15 calendar days. Include outreach activities performed to collect the forms.
      - iii. Number of Excessive Sedation and Loss of Consciousness Adverse Event Forms not received within 30 calendar days. Include outreach activities performed to collect the forms.
      - iv. Results of Excessive Sedation and Loss of Consciousness Adverse Event Forms outstanding from previous reporting periods (if applicable)
8. Safety Surveillance (per reporting period and cumulatively)
- a. Known, or suspected adverse events related to excessive sedation or loss of consciousness are to be reported regardless of outcome. Root cause analyses of whether REMS processes for patient monitoring were followed are to be included. Sources of the reports are to include but not be limited to:
    - i. Post Infusion Form
      - 1. Number of cases of excessive sedation and loss of consciousness reported on the Post Infusion Form, including a calculation of the event incidence.
      - 2. Number of patients who experienced more than one event.
      - 3. Trend analysis of whether adverse events decrease or increase over time
    - ii. Excessive Sedation and Loss of Consciousness Adverse Event Form
    - iii. Adverse events reported in the REMS registry
    - iv. Spontaneous adverse event reports

1. Include the search strategy used to identify cases (via safety database) and specific MedDRA terms used to identify cases of interest
  2. Include a line listing of all cases that includes: manufacturer control number, narrative, assessment of causality, and source of the report
- v. Literature searches
  - vi. Social Media
- b. Include an overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.
9. The requirements for assessments of an approved REMS under section 505-1(g)(3) include, with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

## 7.2 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

The following are the Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs) for Zulresso, if approved:

- PREA PMR 3535-1: Given that adolescents also experience PPD, the Applicant has agreed to conduct a randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of brexanolone in adolescent females ages 15 to less-than-18 years, diagnosed with PPD.
- FDAAA PMR (b) (4): Based on data from published animal studies that reported that administration of drugs that enhance GABAergic inhibition to neonatal rats caused widespread apoptotic neurodegeneration in the developing brain, the Applicant has agreed to conduct an animal neurotoxicity study to determine if these effects will be observed with brexanolone.
- PMC (b) (4): The Applicant will study a (b) (4)
- PMC (b) (4): The Applicant will study the effect of interrupted infusions; (b) (4)

(b) (4)  
 (b) (4) If brexanolone appears safe and effective using this regimen, it may significantly increase the number of settings where patients could receive the drug.

## 8 Discussion of Need for a REMS

Postpartum depression is a serious mental health condition that when untreated can lead to serious outcomes for the mother (i.e. suicide) as well as having a detrimental effect on the child.

There are no treatments currently approved by the FDA for PPD, therefore, there is an unmet medical need in adults with PPD. The clinical data presented in the NDA demonstrated statistically significant reduction in HAM-D score at 60 hours. The clinical reviewer recommends approval of Zulresso based on the efficacy and safety information currently available with a REMS in place at approval.

Zulresso is associated with excessive sedation and sudden LOC. The proposed labeling includes a boxed warning, and a Medication Guide to address these risks. However, DRISK and DPP agree that labeling is not sufficient to mitigate these risks and a REMS is necessary to ensure the benefits outweigh the risks for Zulresso. The safety concerns regarding Zulresso were discussed on October 3, 2018 and January 9, 2019 at the meeting of the REMS Oversight Committee (ROC)<sup>i</sup>. The ROC also concurred that a REMS with ETASU are necessary to ensure the benefits of Zulresso outweigh the risks.

Per the REMS, certified healthcare settings are required to monitor patients for signs and symptoms of excessive sedation, sudden LOC and to assess the patient's oxygen saturation using continuous pulse oximetry. The monitoring is necessary to mitigate the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the ZULRESSO infusion. In addition to monitoring, a certified healthcare setting is required to counsel each patient about the risk, the need for monitoring and enrolling the patient in a registry to better characterize the risks and support safe use. The certified healthcare setting is required to complete the Post Infusion Form for all patients and if an adverse event occurs also complete the Excessive Sedation and Loss of Consciousness Adverse Event Form. Administration of Zulresso and patient monitoring during the infusion will be done by healthcare providers who are trained on the REMS requirements and healthcare setting certification requirements include that the healthcare setting must have the necessary equipment (pump with an alarm, continuous pulse oximetry) for administration. A targeted communication to healthcare providers likely to prescribe the drug will assist in implementation of the REMS. The REMS will ensure that each patient is informed of the adverse events of excessive sedation and loss of consciousness and the need for monitoring during the infusion.

REMS materials required to support the REMS program include a Healthcare Setting Enrollment Form, Patient Enrollment Form, Pharmacy Enrollment Form, Training for Healthcare Settings, Healthcare Setting Knowledge Assessment, Patient Information Guide, Program Overview, Post Infusion Form, Excessive Sedation and Loss of Consciousness Adverse Event Form, Letter for Healthcare Providers, and a REMS Website. The Enrollment forms include attestations for each relevant stakeholder regarding knowledge of the REMS risk, as well as the safe use conditions required before dispensing and administration of the product.

In addition, the Agency determined that the REMS will include letters to likely prescribers and healthcare providers that will provide information regarding the REMS and the risks. Healthcare settings in which the pharmacy and healthcare setting are within the same institution will enroll as a healthcare setting only. The pharmacy requirements in that scenario are the same requirements as those for pharmacies that are not within the same institution as the healthcare setting; The exceptions are the attestations "Review the Program Overview and Submit a Pharmacy Enrollment Form."

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<sup>i</sup> As per the 21<sup>st</sup> Century review process, all REMS with elements to assure safe use (ETASU) are discussed at the REMS Oversight Committee (ROC), which consists of senior level management from the Offices of New Drugs, Surveillance and Epidemiology, and Regulatory Policy.

## 9 Conclusion & Recommendations

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The risk of serious harm resulting from excessive sedation and sudden LOC during the Zulresso infusion is the identified safety concerns for the use of Zulresso. Labeling alone is insufficient to mitigate these risks; therefore, DRISK recommends a REMS consisting of ETASU B (pharmacies and healthcare settings that dispense are specially certified), C (drug to be dispensed in only certain healthcare settings), D (drug dispensed to patients with evidence or other documentation of safe-use conditions), E (each patient using the drug is subject to certain monitoring), and F (each patient using the drug be enrolled in a registry), to ensure that the benefits outweigh the aforementioned risks. The Applicant's amended REMS submission received on March 15 and 18, 2019 has included all the necessary changes communicated on January 18, February 1, March 7, March 14, and March 18, 2019. DRISK is recommending approval of the Zulresso REMS.

## 10 APPENDICES

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### 10.1 REFERENCES

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<sup>1</sup> Shorey S, Chee CYI, Ng ED, Chan YH, Tam WWS, Chong YS. Prevalence and incidence of postpartum depression among healthy mothers: A systematic review and meta-analysis. *J Psychiatric Res* 2018; 104:235-48.

<sup>2</sup> Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatry Association, 2013.

<sup>3</sup> Oates M. Suicide: The leading cause of maternal death, *Br J Psychiatry* 2003; 183:279-81.

<sup>4</sup> Hay, D. F., Pawlby, S., Sharp, D., Asten, P., Mills, A., & Kumar, R. (2001). Intellectual problems shown by 11-year-old children whose mothers had postnatal depression. *Journal of Child Psychology & Psychiatry & Allied Disciplines*, 42(7), 871. Retrieved from [https://auth-lib-unc-edu.libproxy.lib.unc.edu/ezproxy\\_auth.php?url=http://search.ebscohost.com/libproxy.lib.unc.edu/login.aspx?direct=true&db=aph&AN=5557449&site=ehost-live&scope=site](https://auth-lib-unc-edu.libproxy.lib.unc.edu/ezproxy_auth.php?url=http://search.ebscohost.com/libproxy.lib.unc.edu/login.aspx?direct=true&db=aph&AN=5557449&site=ehost-live&scope=site)

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SELENA D READY  
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CYNTHIA L LACIVITA  
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**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 211371   |
| <b>PDUFA Goal Date</b>        | March 19, 2018   |
| <b>OSE RCM #</b>              | 2018-851   |
| <b>Reviewer Name(s)</b>       | Leah Hart, PharmD<br>Kate Oswell   |
| <b>Team Leader</b>            | Selena Ready, PharmD   |
| <b>Division Director</b>      | Cynthia LaCivita, PharmD   |
| <b>Review Completion Date</b> | March 14, 2019   |
| <b>Subject</b>                | Interim Comments for the Proposed REMS for Zulresso  |
| <b>Established Name</b>       | Brexanolone  |
| <b>Trade Name</b>             | Zulresso   |
| <b>Name of Applicant</b>      | Sage Therapeutics, Inc.  |
| <b>Therapeutic Class</b>      | Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator   |
| <b>Formulation(s)</b>         | 5 mg/ml solution   |
| <b>Dosing Regimen</b>         | The dose is weight-based and time-based as follows: <ul style="list-style-type: none"><li>• 4 hours at 30 µg/kg/hour</li><li>• 20 hours at 60 µg/kg/hour</li><li>• 28 hours at 90 µg/kg/hour</li><li>• 4 hours at 60 µg/kg/hour</li><li>• 4 hours at 30 µg/kg/hour</li></ul> |

## 1 Introduction

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The following comments are based on the Agency's review of the proposed REMS for Zulresso submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018, February 15, and March 11, 2019. Sage Therapeutics, Inc. (Applicant) submitted a New Drug Application (NDA) 211371 for Zulresso with the proposed indication to treat post-partum depression. This application is under review in the Division of Psychiatric Products (DPP). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. DRISK agrees that a REMS with ETASU is required and is recommending that a REMS with ETASU B (pharmacy certification), C (healthcare setting certification), D (safe use conditions), E (monitoring), and F (registry) are necessary for the benefits of Zulresso to outweigh the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the Zulresso infusion.

## 2 Comments to the Applicant

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The following comments are based on the Agency's review of the proposed REMS for Zulresso submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018, February 15, and March 11, 2019. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS as a REMS Amendment by Friday, March 15, 2019.

### REMS Document:

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CYNTHIA L LACIVITA  
03/14/2019 03:05:26 PM

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**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 211371   |
| <b>PDUFA Goal Date</b>        | March 19, 2018   |
| <b>OSE RCM #</b>              | 2018-851   |
| <b>Reviewer Name(s)</b>       | Leah Hart, PharmD<br>Kate Oswell   |
| <b>Team Leader</b>            | Selena Ready, PharmD   |
| <b>Division Director</b>      | Cynthia LaCivita, PharmD   |
| <b>Review Completion Date</b> | March 7, 2019  |
| <b>Subject</b>                | Interim Comments for the Proposed REMS for Zulresso  |
| <b>Established Name</b>       | Brexanolone  |
| <b>Trade Name</b>             | Zulresso   |
| <b>Name of Applicant</b>      | Sage Therapeutics, Inc.  |
| <b>Therapeutic Class</b>      | Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator   |
| <b>Formulation(s)</b>         | 5 mg/ml solution   |
| <b>Dosing Regimen</b>         | The dose is weight-based and time-based as follows: <ul style="list-style-type: none"><li>• 4 hours at 30 µg/kg/hour</li><li>• 20 hours at 60 µg/kg/hour</li><li>• 28 hours at 90 µg/kg/hour</li><li>• 4 hours at 60 µg/kg/hour</li><li>• 4 hours at 30 µg/kg/hour</li></ul> |

## 1 Introduction

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The following comments are based on the Agency’s review of the proposed REMS for Zulresso submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018 and February 15, 2019. Sage Therapeutics, Inc. submitted a New Drug Application (NDA) 211371 for Zulresso with the proposed indication to treat post-partum depression. This application is under review in the Division of Psychiatric Products (DPP). The Applicant’s proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Zulresso outweigh the risk of “negative outcomes resulting from loss of consciousness.” DRISK and DPP agree that a REMS with ETASU is required but differ from the Applicant regarding the REMS risks. DRISK and DPP determined that a REMS with ETASU B (pharmacy certification), C (healthcare setting certification), D (safe use conditions), E (monitoring), and F (registry) are necessary for the benefits of Zulresso to outweigh the risk of serious harm resulting from excessive sedation and sudden loss of consciousness during the Zulresso infusion

## 2 Comments to the Applicant

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The following comments are based on the Agency’s review of the proposed REMS for Zulresso submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018 and February 15, 2019. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS as a REMS Amendment by COB on Monday, March 11, 2019. Review of your application and proposed REMS is ongoing; therefore, these comments should not be considered final.

### **REMS Document:**



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SELENA D READY  
03/07/2019 03:14:53 PM

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 211371   |
| <b>PDUFA Goal Date</b>        | March 19, 2018   |
| <b>OSE RCM #</b>              | 2018-851   |
| <b>Reviewer Name(s)</b>       | Leah Hart, PharmD<br>Kate Oswell   |
| <b>Team Leader</b>            | Selena Ready, PharmD   |
| <b>Division Director</b>      | Cynthia LaCivita, PharmD   |
| <b>Review Completion Date</b> | January 31, 2019   |
| <b>Subject</b>                | Interim Comments for the Proposed REMS for Zulresso  |
| <b>Established Name</b>       | Brexanolone  |
| <b>Trade Name</b>             | Zulresso   |
| <b>Name of Applicant</b>      | Sage Therapeutics, Inc.  |
| <b>Therapeutic Class</b>      | Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator   |
| <b>Formulation(s)</b>         | 5 mg/ml solution   |
| <b>Dosing Regimen</b>         | The dose is weight-based and time-based as follows: <ul style="list-style-type: none"><li>• 4 hours at 30 µg/kg/hour</li><li>• 20 hours at 60 µg/kg/hour</li><li>• 28 hours at 90 µg/kg/hour</li><li>• 4 hours at 60 µg/kg/hour</li><li>• 4 hours at 30 µg/kg/hour</li></ul> |

## 1 Introduction

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The following comments are based on the Agency's review of the proposed REMS for Zulresso submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018. Sage Therapeutics, Inc. submitted a New Drug Application (NDA) 211371 for Zulresso with the proposed indication to treat post-partum depression. This application is under review in the Division of Psychiatric Products (DPP). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Zulresso outweigh the risk of negative outcomes resulting from loss of consciousness. DRISK and DPP determined that a REMS with a communication plan and ETASU B (pharmacy certification), C (healthcare setting certification), D (safe use conditions), E (monitoring), and F (registry) are necessary for the benefits of Zulresso to outweigh the risk of serious harm resulting from excessive sedation and loss of consciousness during the Zulresso infusion.

## 2 Comments to the Applicant

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The following comments are based on the Agency's review of the proposed REMS for Zulresso submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS as a REMS Amendment within 14 calendar days. Final clearance of the REMS Document is ongoing; this should not be considered final.

**REMS Document:** Attached is a draft Zulresso REMS Document. As this draft document is still undergoing internal review, this is not to be considered the final REMS Document.

**REMS Appended Materials:** Attached is the draft attestations that could be included in the enrollment forms. The attestations are subject to further internal clearance and should not be considered final. All REMS appended materials must align with both the REMS Document, as well as the final Prescribing Information.

### **Website Screenshots:**

Submit a complete set of updated REMS website screenshots showing all content and functionality of the website. If online education and/or enrollment are an option, you must submit a screenshot(s) of what the new window(s) would look like as part of the functionality of your website submission. This would include the data fields to complete, and the information that pops up for the provider to read.

The updated screenshots should also include a link to access the certified healthcare settings.

### **REMS Supporting Document:**

The Supporting Document should align with the REMS and provide REMS operational details.

A proposed REMS assessment plan must be included in the REMS Supporting Document.

### **Resubmission Instructions:**

Your complete REMS proposal should be submitted as separate documents in the same submission, to include both a Word tracked changes version, a Word clean version, as well as a .pdf version of each of the previously mentioned documents and appended materials.

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SELENA D READY  
02/01/2019 02:55:18 PM

**Division of Risk Management (DRISK)**  
**Office of Medication Error Prevention and Risk Management (OMEPRM)**  
**Office of Surveillance and Epidemiology (OSE)**  
**Center for Drug Evaluation and Research (CDER)**

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|-------------------------------|--|
| <b>Application Type</b>       | NDA  |
| <b>Application Number</b>     | 211371   |
| <b>PDUFA Goal Date</b>        | March 19, 2019   |
| <b>OSE RCM #</b>              | 2018-851   |
| <b>Reviewer Name(s)</b>       | Leah Hart, PharmD<br>Kate Oswell   |
| <b>Team Leader</b>            | Selena Ready, PharmD   |
| <b>Division Director</b>      | Cynthia LaCivita, PharmD   |
| <b>Review Completion Date</b> | January 18, 2018   |
| <b>Subject</b>                | Interim Comments for the Proposed REMS for Zulresso  |
| <b>Established Name</b>       | Brexanolone  |
| <b>Trade Name</b>             | Zulresso   |
| <b>Name of Applicant</b>      | Sage Therapeutics, Inc.  |
| <b>Therapeutic Class</b>      | Neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator   |
| <b>Formulation(s)</b>         | 5 mg/ml solution   |
| <b>Dosing Regimen</b>         | The dose is weight-based and time-based as follows: <ul style="list-style-type: none"><li>• 4 hours at 30 µg/kg/hour</li><li>• 20 hours at 60 µg/kg/hour</li><li>• 28 hours at 90 µg/kg/hour</li><li>• 4 hours at 60 µg/kg/hour</li><li>• 4 hours at 30 µg/kg/hour</li></ul> |

## 1 INTRODUCTION

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The following comments are based on the Agency's review of the proposed REMS for brexanolone 5 mg/mL intravenous (IV) injection, solution (Zulresso) submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018. Sage Therapeutics, Inc. (Applicant) submitted a New Drug Application (NDA) 211371 for Zulresso on April 19, 2018 with the proposed indication to treat post-partum depression (PPD). This application is under review in the Division of Psychiatry Products (DPP). The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments to ensure the benefits of Zulresso outweigh the risk of negative outcomes resulting from loss of consciousness during infusion. DRISK and DPP agree that a REMS with ETASU is required and have determined that a communication plan and ETASU B (pharmacy certification), C (healthcare setting certification), D (safe use conditions), E (monitoring), and F (registry) are necessary for the benefits of Zulresso to outweigh the potential risk.

## 2 COMMENTS TO THE APPLICANT

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The following comments are based on the Agency's review of the proposed REMS for Zulresso submitted to NDA 211371 on November 1, 2018 and amended on November 8, 2018. To facilitate further review, we ask that you revise your REMS proposal based on the following comments and resubmit your complete REMS amendment within 14 calendar days. Review of the REMS Document, Supporting Document, and appended materials is ongoing; therefore these comments should not be considered final.

(b) (4)



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