ZULRESSO™
(brexanolone) injection

US Food and Drug Administration–approved indication
ZULRESSO is indicated for the treatment of postpartum depression (PPD) in adults.1

IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS
Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration.
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).
Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

Please see additional Important Safety Information on page 24 and accompanying full Prescribing Information, including BOXED WARNING, for ZULRESSO starting on page 26.

This publication is designed for payers, formulary committees, or other similar entities with knowledge and expertise in the area of healthcare economics making decisions regarding access, coverage, and reimbursement for ZULRESSO.

This publication for P&T was developed in collaboration with and with support from Sage Therapeutics, Inc.
The Product Profiler

The Product Profiler publication provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler supplies information about pharmacology, clinical studies, FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional pharmacy and therapeutics (P&T) committee considerations, in a convenient package.

About the Authors

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Disclosures

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Please see INDICATION and IMPORTANT SAFETY INFORMATION on page 24 and accompanying FULL PRESCRIBING INFORMATION including BOXED WARNING, for ZULRESSO starting on page 26.
Introduction

This Product Profiler introduces ZULRESSO, an injection for intravenous use in the treatment of postpartum depression (PPD) in adults.\(^1\) ZULRESSO was approved by the US Food and Drug Administration (FDA) on March 19, 2019. The US Drug Enforcement Administration (DEA) completed regulatory status review and placed ZULRESSO in Schedule IV of the Controlled Substances Act through an interim final rule effective June 17, 2019.\(^2\)

PPD is one of the most common medical complications during and after pregnancy.\(^3^-^9\) In the United States, estimates of new mothers identified with PPD each year vary by state from 8% to 20%, with an overall average of 11.5% (Figure 1).\(^3\)

Despite state-mandated screenings and other condition management programs, such as education programs and task forces, that have been implemented for several years in some states, diagnosis rates of PPD still remain low among postpartum mothers.\(^10^-^13\) Mothers with PPD and households with mothers with PPD have been found to have higher medical and pharmaceutical insurer spending than those without PPD.\(^14,15\) The following presents an overview of the disease state and the efficacy and safety considerations for the use of ZULRESSO in adults.
Disease State Overview

Defining PPD

PPD is distinct from “baby blues” owing to the timing, duration, and/or severity of depressive symptoms. A mother with “baby blues” may experience symptoms such as crying, irritability, fatigue, and sadness. The onset of “baby blues” generally peaks within the first few days postdelivery and resolves without treatment in 2 weeks. PPD symptoms may occur during pregnancy or postdelivery. During the same 2-week period of depressed mood or loss of interest or pleasure, other symptoms can include: insomnia or hypersomnia; psychomotor agitation or retardation; fatigue; feelings of worthlessness or excessive/inappropriate guilt; diminished ability to think or indecisiveness; or recurrent suicidal ideation with or without a specific plan or suicide attempt.

Expert opinions vary as to the timing of occurrence of PPD symptoms:
- The American College of Obstetricians and Gynecologists (ACOG) notes that perinatal depression, also known as PPD, includes major and minor depressive episodes that occur during pregnancy or within 12 months of delivery.
- According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a major depressive episode or major depression can be qualified as peripartum if onset occurs during pregnancy or within 4 weeks of delivery.

There are multiple hypotheses about the mechanism of disease of PPD. Risk factors associated with PPD include history of depression and/or family depression, sleep disturbances, history of trauma, chronic stress, and low socioeconomic status.

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Figure 1.
Prevalence of PPD

In the United States, estimates of new mothers identified with PPD each year vary by state from 8% to 20%, with an overall average of 11.5%

These estimates suggest that >400,000 women may experience PPD each year

Approximately half of patients experiencing PPD are diagnosed

Each mom icon represents 20,000 women.

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*Rate of diagnosed patients may vary between 40% and 70%.

*bSeverities estimates are based upon data from the McCabe-Beane and PACT Consortium references. Point estimates and ranges of severity for mild (20%, 18%–22%), moderate (55%, 50%–60%), and severe (25%, 20%–30%) PPD symptoms were generated.
Screening for PPD

Screening for PPD has been recommended during both pregnancy and the postpartum period to help clinicians identify women who are at an increased risk for PPD or who may already have PPD.9,17,36,37

Screening for PPD can be critical to providing timely care for mothers; it is recommended in guidelines (Table 1) and mandated by a growing number of states (Figure 2).9,17,36,37,40-44

Numerous states have enacted more progressive policies aimed at addressing the many challenges associated with perinatal behavioral health needs, while also encouraging routine PPD screening by healthcare providers (HCPs); see Figure 2 below.

<table>
<thead>
<tr>
<th>Table 1. Multiple Professional Societies Recommend Screening for PPD</th>
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<tbody>
<tr>
<td><strong>Recommendations for Screening for PPD</strong></td>
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<tr>
<td>ACOG</td>
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<tr>
<td>AAP</td>
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<tr>
<td>AAP</td>
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<tr>
<td>USPSTF</td>
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</table>


**Figure 2.**
State-Mandated PPD Screening and Educational Initiatives for Perinatal Mothers38-59
There is no universally used screening instrument to identify patients at risk for PPD. ACOG recommends using a validated screening tool; some tools include: the Edinburgh Postnatal Depression Scale (EPDS), Postpartum Depression Screening Scale (PDSS), Patient Health Questionnaire (PHQ-9), Beck Depression Inventory (BDI), Beck Depression Inventory-II (BDI-II), Center for Epidemiologic Studies Depression Scale (CES-D), and Zung Self-Rating Depression Scale. Diagnosis of PPD can only be made with a clinical assessment of the patient by a healthcare professional. Obstetrician/gynecologists (OB/GYNs), maternal-fetal medicine physicians, and primary care providers see the patient throughout pregnancy and at 6 weeks postpartum. OB/GYNs and other women's health providers are qualified to enable women to access clinical and social resources as they navigate the transition from pregnancy to parenthood.

Figure 3.
Healthcare Burden for Mothers With PPD

Mothers with PPD have 11 more outpatient visits and greater prescription drug use versus mothers without PPD per year after childbirth. Mothers with PPD incur 90% higher health services expenditures than mothers without PPD. Households with a mother with PPD incur 22% higher medical and pharmaceutical insurer spending than households with a mother without PPD in the first year after childbirth.

Burden of PPD

Perinatal women are often reluctant to seek help for symptoms related to PPD due to social stigma and barriers to available treatment options. Barriers may include reluctance to acknowledge mental health concerns to family, friends, or HCPs due to shame, guilt, or the fear of potential consequences. Additional barriers may include lack of access to mental health resources or knowledge about where to seek them and lack of access to childcare during postpartum visits.

PPD can also add to the burden on the healthcare system, as mothers with PPD can incur higher health services expenditures than mothers without PPD (Figure 3).

Historical Unmet Needs in PPD

Treatment options for mothers with PPD may depend on the severity of symptoms, current and previously used medications, patient preference, and medical history. Prior to the launch of ZULRESSO, there were no FDA-approved therapies for the treatment of PPD. Historically, commonly used treatment options included nonpharmacological interventions such as psychosocial treatment and psychotherapy, as well as pharmacotherapy with antidepressants used off-label.
ZULRESSO™ (brexanolone) injection: the First and Only Treatment Specifically Indicated for PPD in Adults

ZULRESSO is a single-use, continuous intravenous injection that was approved by the FDA on March 19, 2019, for the treatment of PPD in adults. On June 17, 2019, the DEA placed ZULRESSO into Schedule IV, under the Controlled Substances Act.

ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS because excessive sedation and sudden loss of consciousness can result in serious harm.

Indication, Dosage, and Administration

Indications and Usage
ZULRESSO is indicated for the treatment of PPD in adults.

Dosage and Administration
Important Considerations Prior to Initiating and During Therapy:
- A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the ZULRESSO infusion
- Monitor patients for hypoxia using continuous pulse oximetry equipped with an alarm. Assess for excessive sedation every 2 hours during planned, nonsleep periods
- Initiate ZULRESSO treatment early enough during the day to allow for recognition of excessive sedation
If excessive sedation occurs at any time during the infusion, stop the infusion until symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.

Figure 4. Recommended Dosage

ZULRESSO is administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows:
Preparation and Storage Instructions

ZULRESSO is supplied in vials as a concentrated solution that requires dilution prior to administration. After dilution, the product can be stored in infusion bags under refrigerated conditions for up to 96 hours. However, given that the diluted product can be used for only 12 hours at room temperature, each 60-hour infusion will require the preparation of at least 5 infusion bags. See Table 2 for ZULRESSO preparation steps.

Diluted ZULRESSO Storage Instructions

- If not used immediately after dilution, store under refrigerated conditions for up to 96 hours. Prolonged storage at room temperature may support adventitious microbial growth
- Each prepared bag of diluted ZULRESSO may be used for up to 12 hours of infusion time at room temperature. Discard any unused ZULRESSO after 12 hours of infusion

Administration Instructions

Prior to administration, ZULRESSO must be diluted. The following are important administration instructions:

- Use a programmable peristaltic infusion pump to ensure accurate delivery of ZULRESSO
- Administer ZULRESSO via a dedicated line. Do not inject other medications into the infusion bag or mix with ZULRESSO
- Fully prime infusion administration sets with admixture before inserting into the pump and connecting to the venous catheter
- Use a PVC, non-DEHP, nonlatex infusion set. Do not use in-line filter infusion sets

Recommendations in Patients With End Stage Renal Disease (ESRD)

Treatment with ZULRESSO is not recommended in patients with ESRD with eGFR of <15 mL/minute/1.73 m².

Dosage Forms and Strength

Injection: 100 mg/20 mL (5 mg/mL) single-dose vial.

How Supplied and Storage Conditions

ZULRESSO injection (NDC 72152-547-20) is supplied as 100 mg brexanolone in 20 mL (5 mg/mL) single-dose vials containing a sterile, preservative-free, clear, colorless solution. The undiluted ZULRESSO product should be stored at 2°C to 8°C (36°F to 46°F). Do not freeze. Store protected from light. The diluted product in the infusion bag can be used at room temperature for up to 12 hours. If the diluted product is not used immediately after dilution, store under refrigerated conditions for up to 96 hours.

Table 2. Product Preparation

Prepare according to the following steps using aseptic technique:

- Visually inspect the vials of ZULRESSO for particulate matter and discoloration prior to administration. ZULRESSO is a clear, colorless solution. Do not use if the solution is discolored or particulate matter is present
- The 60-hour infusion will generally require the preparation of 5 infusion bags. Additional bags will be needed for patients weighing ≥90 kg
- For each infusion bag:
  - Prepare and store in a polyolefin, non-DEHP, nonlatex bag, only. Dilute in the infusion bag immediately after the initial puncture of the drug product vial
  - Withdraw 20 mL of ZULRESSO from the vial and place in the infusion bag. Dilute with 40 mL of Sterile Water for Injection, and further dilute with 40 mL of 0.9% Sodium Chloride Injection (total volume of 100 mL) to achieve a target concentration of 1 mg/mL
  - Immediately place the infusion bag under refrigerated conditions until use
Chemistry and Clinical Pharmacology

Description
ZULRESSO contains brexanolone, a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator that is chemically identical to endogenous allopregnanolone.

ZULRESSO injection is a sterile, clear, colorless, and preservative-free solution. ZULRESSO 5 mg/mL is hypertonic and must be diluted prior to administration as an intravenous infusion. Each mL of solution contains 5 mg of brexanolone, 250 mg of betadex sulfobutyl ether sodium, 0.265 mg of citric acid monohydrate, 2.57 mg of sodium citrate dihydrate, and water for injection. Hydrochloric acid or sodium hydroxide may be used during manufacturing to adjust pH.

Clinical Pharmacology

Mechanism of Action
The mechanism of action of brexanolone in the treatment of PPD in adults is not fully understood but is thought to be related to its positive allosteric modulation of GABA_A receptors.

Pharmacodynamics
Brexanolone potentiated GABA-mediated currents from recombinant human GABA_A receptors in mammalian cells expressing α1β2γ2 receptor subunits, α4β3δ receptor subunits, and α6β3δ receptor subunits. Brexanolone exposure-response relationships and the time course of pharmacodynamics response are unknown.

Pharmacokinetics
Brexanolone exhibited dose-proportional pharmacokinetics over a dosage range of 30 mcg/kg/hour to 270 mcg/kg/hour (3 times the maximum recommended dosage). Mean steady state exposure at 60 mcg/kg/hour and 90 mcg/kg/hour was around 52 ng/mL and 79 ng/mL, respectively.

Distribution: The volume of distribution of brexanolone was approximately 3 L/kg, suggesting extensive distribution into tissues. Plasma protein binding was greater than 99% and is independent of plasma concentrations.

Elimination: The terminal half-life of brexanolone was approximately 9 hours. The total plasma clearance of brexanolone is approximately 1 L/hour/kg.

Metabolism: Brexanolone is extensively metabolized by non-CYP based pathways via 3 main routes: keto-reduction (AKRs), glucuronidation (UGTs), and sulfation (SULTs). There are 3 major circulating metabolites that are pharmacologically inactive and do not contribute to the overall efficacy of ZULRESSO.

Excretion: Following administration of radiolabeled brexanolone, 47% was recovered in feces (primarily as metabolites) and 42% in urine (with less than 1% as unchanged brexanolone).

Specific Populations: No clinically significant differences in the pharmacokinetics of brexanolone were observed based on renal impairment (severe) study or hepatic impairment (mild, moderate, severe) study. The effect of ESRD (eGFR <15 mL/minute/1.73 m^2) on brexanolone pharmacokinetics is unknown. However, use of ZULRESSO in patients with ESRD should be avoided.

Clinical Studies

Study Design and Participants
The clinical evidence for the efficacy of ZULRESSO in the treatment of PPD was demonstrated in 2 multicenter, randomized, double-blind, placebo-controlled phase 3 studies (referred to as Studies 1 and 2) at 30 clinical research centers and specialized psychiatric units in the United States. The studies enrolled women with PPD who met the Diagnostic and Statistical Manual of Mental Disorders criteria for a major depressive episode (DSM-4) with onset of symptoms in the third trimester or within 4 weeks of delivery:

- **Study 1** (NCT02942004) included patients with severe PPD (Hamilton Depression Rating Scale [HAM-D] total score ≥26)
- **Study 2** (NCT02942017) included patients with moderate PPD (HAM-D total score of 20 to 25)

Key eligibility criteria are presented in Table 3.
Table 3.
Patient Eligibility Criteria \(^{1,67}\)

<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
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</thead>
<tbody>
<tr>
<td>• Adult women ages 18 to 45</td>
<td>• Active psychosis</td>
</tr>
<tr>
<td>• Major depressive episode that began no earlier than the third trimester and no later than the first 4 weeks following delivery as confirmed by Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I)</td>
<td>• Experienced renal failure requiring dialysis, fulminant hepatic failure, anemia (baseline hemoglobin &lt;10 g/dL)</td>
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<tr>
<td>• Within 6 months postpartum at time of enrollment</td>
<td>• Known allergy to allopregnanolone or to progesterone</td>
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</table>

Additional Inclusion and Exclusion Requirements

- Subjects could be on stable psychotropics, but they had to be willing to delay the start of any new pharmacotherapy regimens until the study drug infusion and 72-hour assessments were completed
- Subjects must have ceased breastfeeding at screening or, if still breastfeeding at screening, must have agreed to cease breastfeeding before receiving the study drug until 4 days after the end of the infusion

Randomization and Procedures \(^{1,67}\)

Eligible patients in Study 1 were randomized 1:1:1 to receive ZULRESSO injection of 90 mcg/kg/hour, 60 mcg/kg/hour, or placebo infusion. In Study 2, eligible patients were randomized 1:1 to ZULRESSO 90 mcg/kg/hour or placebo. Across both studies, patients received a 60-hour continuous intravenous infusion of ZULRESSO or placebo and were then followed for 4 weeks, with clinical and safety assessments at multiple time points (Figure 5).

To achieve a titration target dose of 90 mcg/kg/hour among patients in both Study 1 and 2, each patient received a single continuous infusion of study drug over 60 hours using the following dosing schedule:

- 30 mcg/kg/hour for 4 hours
- 60 mcg/kg/hour for 20 hours
- 90 mcg/kg/hour for 28 hours
- 60 mcg/kg/hour for 4 hours
- 30 mcg/kg/hour for 4 hours

For one cohort in Study 1, titration to a target dosage of 60 mcg/kg/hour was achieved using the following schedule: 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 48 hours, and then 30 mcg/kg/hour for 4 hours.

Figure 5.
ZULRESSO Study Design

2 Clinical Studies (N=226) \(^{a}\)

Study 1 (N=122)
Severe PPD
Baseline HAM-D score of ≥26

Study 2 (N=104)
Moderate PPD
Baseline HAM-D score 20-25

60-hour infusion with post-treatment follow-ups at day 7 and day 30

Randomization (1:1:1)

ZULRESSO 90 mcg/kg/hour

ZULRESSO 60 mcg/kg/hour

Placebo

Randomization (1:1)

ZULRESSO 90 mcg/kg/hour

Placebo

\(^{a}\)Intention to treat population.
Demographics and Baseline Characteristics

Demographic and baseline disease characteristics were generally similar across treatment groups in the pooled studies 1 and 2. Most patients were White (63%) or Black (34%); 18% of patients identified as Hispanic or Latina; the average age of women receiving ZULRESSO was 28 years. Most patients (76%) had onset of PPD symptoms within 4 weeks after delivery, with the remainder having onset during the third trimester. Baseline oral antidepressant use was reported for 23% of patients.

Outcomes

In pooled studies 1 and 2, the primary endpoint was the mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion (hour 60). A prespecified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at day 30. Additional outcome measures are summarized in Table 4.

<table>
<thead>
<tr>
<th>Table 4. Outcome Measures for Secondary Endpoints&lt;sup&gt;1,67&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>Prespecified Secondary Efficacy Endpoint</strong></td>
</tr>
<tr>
<td>• Mean change from baseline in HAM-D total score at day 30</td>
</tr>
<tr>
<td><strong>Other Endpoints</strong></td>
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<tr>
<td>• Clinical Global Impression (CGI) change from baseline at various time points</td>
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<tr>
<td>• Montgomery Åsberg Depression Rating Scale (MADRS)</td>
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<tr>
<td>• HAM-D individualized item and subscale scores</td>
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<tr>
<td>• Generalized Anxiety Disorder 7-item Scale (GAD-7)</td>
</tr>
<tr>
<td>• Edinburgh Postnatal Depression Scale (EPDS)</td>
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<tr>
<td>• Patient Health Questionnaire (PHQ-9)</td>
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</tbody>
</table>

Results<sup>1,67</sup>

Across both studies, 226 patients—with a total of 122 patients in Study 1 and 104 patients in Study 2—were randomly assigned to either ZULRESSO or placebo (Figure 5). In both placebo-controlled studies, titration to the target dose of ZULRESSO 90 mcg/kg/hour was superior to placebo in improvement of depressive symptoms.

Study 1

At the completion of the 60-hour infusion, ZULRESSO had a statistically significant reduction in depressive symptoms as measured by the HAM-D total score (Table 5). The LS mean reduction from baseline in HAM-D total score at hour 60 was 19.5 (SE 1.2) in the ZULRESSO 60 mcg/kg/hour group and 17.7 (1.2) in the 90 mcg/kg/hour group, compared to 14.0 (1.1) in the placebo group.

The LS mean reduction from baseline in HAM-D total score for the 60 mcg/kg/hour group at day 30 was 19.5 points (SE 1.4) and at hour 60 was 19.5 points (1.2). The LS mean reduction from baseline in HAM-D total score for the 90 mcg/kg/hour group at day 30 was 17.6 points (SE 1.4) and at hour 60 was 17.7 points (1.2). The LS mean reduction from baseline in HAM-D total score for the placebo group at day 30 was 13.8 points (SE 1.3) and at hour 60 was 14.0 points (1.1). The reduction in HAM-D total scores from baseline at day 30 was significantly higher in the 60 mcg/kg/hour (P=0.0044) and 90 mcg/kg/hour groups (P=0.0481) than in the placebo group (Figure 6).

Study 2

The completion of infusion at 60 hours resulted in a mean reduction from baseline in HAM-D total score of 14.6 (SE 0.8) in the 90 mcg/kg/hour group compared to 12.1 (0.8) in the placebo group.

The LS mean reduction from baseline HAM-D total score at day 30 was 14.7 points (SE 1.0) in the ZULRESSO 90 mcg/kg/hour group, which was similar to results shown at hour 60. The placebo group improved the HAM-D total score after day 7, with no significant difference identified in HAM-D total scores between the ZULRESSO 90 mcg/kg/hour and placebo groups at day 30.

Durable Therapeutic Effect

Treatment with ZULRESSO showed durable therapeutic effect with response maintained for up to 30 days after infusion.
Table 5.
Results for the Primary Endpoint—HAM-D Total Score (Studies 1 and 2)\(^1\)

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group (#ITT Subject)</th>
<th>Primary Endpoint: Change From Baseline in HAM-D Total Score at Hour 60</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean Baseline Score (SD)</td>
</tr>
<tr>
<td>1</td>
<td>ZULRESSO target dosage 90 mcg/kg/hour (n=41)(^a)</td>
<td>28.4 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=43)</td>
<td>28.6 (2.5)</td>
</tr>
<tr>
<td></td>
<td>ZULRESSO target dosage 60 mcg/kg/hour (n=38)(^a)</td>
<td>29.0 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=43)</td>
<td>28.6 (2.5)</td>
</tr>
<tr>
<td>2</td>
<td>ZULRESSO target dosage 90 mcg/kg/hour (n=51)(^a)</td>
<td>22.6 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=53)</td>
<td>22.7 (1.6)</td>
</tr>
</tbody>
</table>

\(^a\)Statistically significant after multiplicity adjustments.
CI=confidence interval; ITT=intention to treat; LS=least squares; SD=standard deviation; SE=standard error.

Figure 6.
Change From Baseline in HAM-D Total Score Over Time (Days) in Study 1\(^1\)
Product Profiler: Zulresso™ (Brexanolone) Injection

Safety Considerations

Warnings and Precautions

Excessive Sedation and Sudden Loss of Consciousness:
In clinical studies, Zulresso caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of Zulresso-treated patients compared to 0% of placebo-treated patients). Some patients 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). Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. All patients with loss of or altered state of consciousness recovered with dose interruption. 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.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. 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. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of Zulresso have dissipated. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness. Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, Zulresso is available only through a REMS called the Zulresso REMS.

Suicidal Thoughts and Behaviors: In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and other antidepressant classes) that included approximately 77,000 adult patients and 4500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). Zulresso does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to Zulresso, the risk of developing suicidal thoughts and behaviors with Zulresso is unknown. Consider changing the therapeutic regimen, including discontinuing Zulresso, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

Adverse Reactions

Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to Zulresso in 140 patients (the safety also includes patients from a phase 2 randomized, placebo-controlled study) with PPD. A titration to a target dosage of 90 mcg/kg/hour was evaluated in 102 patients and a titration to a target dose of 60 mcg/kg/hour was evaluated in 38 patients; patients were then followed for 4 weeks.

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush (Table 6).

Adverse Reactions Leading to Discontinuation, Dosage Interruption, or Dosage Reduction: In the pooled placebo-controlled studies, the incidence of patients who discontinued due to any adverse reaction was 2% of Zulresso-treated patients compared to 1% of placebo-treated patients. The adverse reactions leading to treatment...
discontinuation in ZULRESSO-treated patients were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion site pain. The incidence of patients who had an interruption or reduction of the dosage due to any adverse reaction was 7% of ZULRESSO-treated patients compared to 3% of placebo-treated patients. The adverse reactions leading to dose reduction or interruption in ZULRESSO-treated patients were sedation-related (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site events, changes in blood pressure, or medication error due to infusion pump malfunction. Three ZULRESSO-treated patients who had a dosage interruption because of loss of consciousness subsequently resumed and completed treatment after resolution of symptoms; 2 patients who had dosage interruption because of loss of consciousness did not resume the infusion. Table 6 presents the adverse reactions that occurred in ZULRESSO-treated PPD patients at a rate of at least 2% and at a higher rate than in the placebo-treated patients during the 60-hour treatment period.

Table 6.  
Adverse Reactions in Placebo-Controlled Studies in Patients With PPD Reported in ≥2% of ZULRESSO-Treated Patients and Greater Than Placebo-Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=107)</th>
<th>Maximum Dosage 60 mcg/kg/hour (n=38)</th>
<th>Maximum Dosage 90 mcg/kg/hour (Recommended dosage) (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>–</td>
<td>–</td>
<td>3%</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>–</td>
<td>–</td>
<td>2%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>–</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness, presyncope, vertigo</td>
<td>7%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>–</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Sedation, somnolence</td>
<td>6%</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing, hot flush</td>
<td>–</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Drug Interactions

Central Nervous System (CNS) Depressants:
Concomitant use of ZULRESSO with CNS depressants (eg, opioids, benzodiazepines) may increase the likelihood or severity of adverse reactions related to sedation.

Antidepressants:
In the placebo-controlled studies, a higher percentage of ZULRESSO-treated patients who used concomitant antidepressants reported sedation-related events.

Use in Specific Populations

Pregnancy:
Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have background risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Lactation:
Available data from a lactation study in 12 women indicate that ZULRESSO is transferred to breast milk in nursing mothers.
- The relevant infant dose (RID) is low; 1% to 2% of the maternal weight-adjusted dose
- ZULRESSO has a low oral bioavailability (<5%) in adults; therefore, infant exposure is expected to be low
- There were no reports of effects of ZULRESSO on milk production
- There are no data on the effects of ZULRESSO on a breastfed infant
- Available data on the use of ZULRESSO during lactation do not suggest a significant risk of adverse reactions in breastfed infants from exposure to ZULRESSO
- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition

Pediatric Use:
The safety and effectiveness of ZULRESSO in pediatric patients have not been established.

Geriatric Use:
PPD is a condition associated with pregnancy; there is no geriatric experience with ZULRESSO.

Hepatic Impairment:
Dosage adjustment in patients with hepatic impairment is not necessary. Modest increases in exposure to unbound brexanolone and modest decreases in exposure to total brexanolone were observed in patients with moderate to severe hepatic impairment (Child-Pugh ≥7) with no associated change in tolerability.

Renal Impairment:
No dosage adjustment is recommended in patients with mild (eGFR 60 to 89 mL/minute/1.73 m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²) or severe (eGFR 15 to 29 mL/minute/1.73 m²) renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of <15 mL/minute/1.73 m² because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium.

Drug Abuse and Dependence

Controlled Substance:
ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

Abuse:
In a human abuse potential study, 90 mcg/kg, 180 mcg/kg (2 times the maximum recommended infusion rate), and 270 mcg/kg (3 times the maximum recommended infusion rate) ZULRESSO infusions over a 1-hour period were compared to oral alprazolam administration (1.5 mg and 3 mg). On positive subjective measures of “drug liking,” “overall drug liking,” “high,” and “good drug effects,” the 90 mcg/kg dosage produced scores that were similar to placebo. Scores on these positive subjective measures for both dosages of ZULRESSO 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for ZULRESSO 270 mcg/kg dosage were similar to those produced by both doses of alprazolam. In this study, 3% of subjects administered ZULRESSO 90 mcg/kg and 13% administered ZULRESSO 270 mcg/kg reported euphoric mood, compared to none administered placebo during the 1-hour administration.

Dependence:
In the PPD clinical studies conducted with ZULRESSO, end of treatment occurred through tapering. Thus, in these studies it was not possible to assess whether abrupt discontinuation of ZULRESSO produced withdrawal symptoms indicative of physical dependence. It is recommended that ZULRESSO be tapered according to the dosage recommendations, unless symptoms warrant immediate discontinuation.
**Overdosage**

There is limited clinical trial experience regarding human overdosage with ZULRESSO. In premarketing clinical studies, 2 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. In case of overdosage, stop the infusion immediately and initiate supportive measures as necessary. Brexanolone is rapidly cleared from plasma.

**Nonclinical Toxicology**

**Carcinogenesis:** Carcinogenicity studies of brexanolone have not been performed.

**Mutagenesis:** Brexanolone was not genotoxic when tested in an in vitro microbial mutagenicity (Ames) assay, an in vitro micronucleus assay in human peripheral blood lymphocytes, and an in vivo rat bone marrow micronucleus assay.

**Impairment of Fertility:** Treatment of female and male rats with brexanolone at doses equal to and greater than 30 mg/kg/day, which is associated with 2 times the plasma levels at the maximum recommended human dose (MRHD) of 90 mcg/kg/hour, caused impairment of female and male fertility and reproduction.
PPD is one of the most common medical complications during and after pregnancy, with estimates of new mothers identified with PPD each year varying from 8% to 20%. While mandated PPD screenings are in place in a handful of states, diagnosis rates still remain low, and only half of patients experiencing symptoms of PPD are diagnosed. Treatment options for mothers with PPD may depend on the severity of symptoms, current and previously used medications, patient preference, and medical history. Historically, the most commonly used treatment options included nonpharmacological interventions, such as psychosocial treatment and psychotherapy, as well as pharmacotherapy with antidepressants used off-label. ZULRESSO is the first and only FDA-approved treatment for PPD (Table 7). ZULRESSO has demonstrated efficacy results from 2 phase 3 studies and safety results from 3 studies for the treatment of PPD in adults. Patients in the ZULRESSO treatment arms (90 mcg/kg/hour and 60 mcg/kg/hour) achieved the primary endpoint of mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion, with a statistically significant reduction in PPD severity in 2.5 days. In both placebo-controlled studies, titration to the recommended target dose of 90 mcg/kg/hour was significantly superior to placebo in the reduction of depressive symptoms. The group treated with ZULRESSO with a titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms.

The management of PPD has included psychological therapy as a first-line option, with no defined time to response, followed by pharmacologic options for patients with moderate to severe PPD or for those who failed to respond to psychological treatment. Pharmacological treatment options included:

- SSRIs
- Serotonin and norepinephrine reuptake inhibitors (SNRIs)
- Monoamine oxidase inhibitors (MAOIs)
- Tricyclic antidepressants (TCAs)

SSRIs are the most commonly prescribed antidepressant; however, not 1 antidepressant has shown greater benefit over another in the treatment of PPD, and, in fact, data suggest that there is little difference in the effectiveness of pharmacologic over psychologic and/or psychosocial treatment.
When choosing an appropriate pharmacologic treatment for new mothers, considerations include the effect of the antidepressant on lactation. Physicians often advise against breastfeeding while on antidepressants, because antidepressants are excreted into breastmilk and the effects to the infant are unclear.

Although ZULRESSO is transferred into breastmilk, the RID is low and the low oral bioavailability of ZULRESSO in adults suggests low exposure to infants. ZULRESSO study data do not suggest a significant risk of adverse effects on breastfed infants. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.1

In clinical studies, ZULRESSO caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients). Some patients 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). Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS. See Table 8 for notable ZULRESSO REMS requirements.1

<table>
<thead>
<tr>
<th>Table 8. Notable ZULRESSO REMS Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS</td>
</tr>
<tr>
<td>• Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS</td>
</tr>
<tr>
<td>• Patients must be enrolled in the REMS program prior to administration of ZULRESSO</td>
</tr>
<tr>
<td>• Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies</td>
</tr>
</tbody>
</table>

ZULRESSO may be a first-line treatment for women with PPD1 and should be considered as a formulary option for appropriate patients.
Conclusions

Approximately 1 in 9 women suffer from postpartum depressive symptoms; the onset of PPD symptoms can occur during pregnancy or up to 1 year after giving birth. Mothers suffering from PPD may experience symptoms such as depressed mood, diminished interest, psychomotor agitation, feelings of worthlessness or excessive guilt, diminished ability to think or concentrate and indecisiveness, or thoughts of suicidal ideation and/or attempts.

Perinatal women are often reluctant to seek help for symptoms related to PPD due to social stigma and barriers to available treatment options. Prior to the availability of ZULRESSO in June 2019, there were no FDA-approved therapies indicated for the treatment of PPD. Commonly used treatment options included nonpharmacological interventions, such as psychosocial treatment and psychotherapy, as well as pharmacotherapy with antidepressants used off-label.

In both placebo-controlled studies, titration to the target dose of ZULRESSO 90 mcg/kg/hour was superior to placebo in improvement of depressive symptoms. At the completion of the 60-hour infusion, ZULRESSO had a significant reduction in depressive symptoms as measured by the HAM-D total score. Treatment with ZULRESSO showed durable therapeutic effect with response maintained at day 30. Following intravenous administration of brexanolone, plasma concentrations decline with a terminal half-life of approximately 9 hours and are cleared with total plasma clearance of approximately 1 L/hour/kg.

ZULRESSO is available only through a restricted program called the ZULRESSO REMS. The ZULRESSO REMS allows for the appropriate monitoring and management of the risk of excessive sedation and sudden loss of consciousness during the ZULRESSO infusion. For more information on ZULRESSO and the ZULRESSO REMS, please visit www.zulressohcp.com.

ZULRESSO is the first and only FDA-approved therapy for PPD. ZULRESSO has demonstrated efficacy results from 2 phase 3 studies and safety results from 3 studies for the treatment of PPD in adults. Patients in both ZULRESSO treatment arms (90 mcg/kg/hour and 60 mcg/kg/hour) achieved the primary endpoint with a significant reduction in PPD severity in 2.5 days and maintained a therapeutic effect at day 30. ZULRESSO should be considered as a formulary option, as it is a new treatment option for patients with PPD.
References


33. Data on file, Epidemiology PPD Data.


65. Data on file, Partnership for Health Analytic Research.


INDICATION
ZULRESSO™ (brexanolone) CIV is indicated for the treatment of postpartum depression (PPD) in adults.

IMPORTANT SAFETY INFORMATION for ZULRESSO

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS
Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration. 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).
Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS.

WARNINGS AND PRECAUTIONS

Excessive Sedation and Sudden Loss of Consciousness
In clinical studies, 5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients experienced sedation and somnolence that required dose interruption or reduction. Loss of consciousness or altered state of consciousness was reported in 4% of ZULRESSO-treated patients compared with 0% of placebo-treated patients.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. 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. Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed. Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving, after infusion until any sedative effects of ZULRESSO have dissipated.

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS)
ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm.

Notable requirements of the ZULRESSO REMS include:
- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or call 1-844-472-4379.

Suicidal Thoughts and Behaviors
In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that include approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD).
ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. If depression becomes worse or patients experience emergent suicidal thoughts and behaviors, consider changing the therapeutic regimen, including discontinuing ZULRESSO.

**Adverse Reactions**
The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

**Use in Specific Populations**

- **Pregnancy:** Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants, including ZULRESSO, during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at [https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/](https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/)

- **Lactation:** Brexanolone is transferred to breastmilk in nursing mothers. There are no data on the effects of ZULRESSO on a breastfed infant. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

- **Pediatric Use:** The safety and effectiveness of ZULRESSO in pediatric patients have not been established.

- **Renal Impairment:** No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment. Avoid use of ZULRESSO in patients with end stage renal disease (ESRD).

**Controlled Substance**
ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

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Please also see **Full Prescribing Information including Boxed Warning** for ZULRESSO, starting on page 26.

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZULRESSO safely and effectively. See full prescribing information for ZULRESSO.

ZULRESSO™ (bexanolone) injection, for intravenous use, CIV

Initial U.S. Approval: 2019

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

See full prescribing information for complete boxed warning.

• Patients are at risk of excessive sedation or sudden loss of consciousness during administration of ZULRESSO. (5.1)
• 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). (5.1)
• ZULRESSO is available only through a restricted program called the ZULRESSO REMS. (5.1, 5.2)

INDICATIONS AND USAGE

ZULRESSO is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator indicated for the treatment of postpartum depression (PPD) in adults. (1)

DOSAGE AND ADMINISTRATION

• A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the infusion. (2.1)
• Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows (2.2):
  o 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
  o 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
  o 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)
  o 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
  o 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour
• Dilution required prior to administration. (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/20 mL (5 mg/mL) single-dose vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Suicidal Thoughts and Behaviors: Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose PPD becomes worse or who experience emergent suicidal thoughts and behaviors. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sage Therapeutics, Inc. at 1-844-4-SAGERX (1-844-472-4379) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

• Pregnancy: May cause fetal harm. (8.1)
• Avoid use in patients with end stage renal disease (ESRD). (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 6/2019
FULL PRESCRIBING INFORMATION

WARNING: EXCESSIVE SEDATION AND SUDDEN LOSS OF CONSCIOUSNESS

Patients treated with ZULRESSO are at risk of excessive sedation or sudden loss of consciousness during administration [see Warnings and Precautions (5.1)].

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) [see Warnings and Precautions (5.1)].

Because of these risks, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS [see Warnings and Precautions (5.2)].

1 INDICATIONS AND USAGE

ZULRESSO is indicated for the treatment of postpartum depression (PPD) in adults [see Clinical Studies (14)].

2 DOSAGE AND ADMINISTRATION

2.1 Important Considerations Prior to Initiating and During Therapy

A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the ZULRESSO infusion.

Monitor patients for hypoxia using continuous pulse oximetry equipped with an alarm. Assess for excessive sedation every 2 hours during planned, non-sleep periods [see Warnings and Precautions (5.1)].

Initiate ZULRESSO treatment early enough during the day to allow for recognition of excessive sedation [see Warnings and Precautions (5.1)].

2.2 Recommended Dosage

Administer ZULRESSO as a continuous intravenous (IV) infusion over a total of 60 hours (2.5 days) as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (a reduction in dosage to 60 mcg/kg/hour may be considered during this time period for patients who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
• 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

If excessive sedation occurs at any time during the infusion, stop the infusion until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.

2.3 Preparation and Storage Instructions

ZULRESSO is supplied in vials as a concentrated solution that requires dilution prior to administration. After dilution, the product can be stored in infusion bags under refrigerated conditions for up to 96 hours. However, given that the diluted product can be used for only 12 hours at room temperature, each 60-hour infusion will require the preparation of at least five infusion bags.

Prepare according to the following steps using aseptic technique:

• Visually inspect the vials of ZULRESSO for particulate matter and discoloration prior to administration. ZULRESSO is a clear, colorless solution. Do not use if the solution is discolored or particulate matter is present.

• The 60-hour infusion will generally require the preparation of five infusion bags. Additional bags will be needed for patients weighing ≥ 90 kg.

• For each infusion bag:
  o Prepare and store in a polyolefin, non-DEHP, nonlatex bag, only. Dilute in the infusion bag immediately after the initial puncture of the drug product vial.
  o Withdraw 20 mL of ZULRESSO from the vial and place in the infusion bag. Dilute with 40 mL of Sterile Water for Injection, and further dilute with 40 mL of 0.9% Sodium Chloride Injection (total volume of 100 mL) to achieve a target concentration of 1 mg/mL.
  o Immediately place the infusion bag under refrigerated conditions until use.

Diluted ZULRESSO storage instructions:

• If not used immediately after dilution, store under refrigerated conditions for up to 96 hours. Prolonged storage at room temperature may support adventitious microbial growth.

• Each prepared bag of diluted ZULRESSO may be used for up to 12 hours of infusion time at room temperature. Discard any unused ZULRESSO after 12 hours of infusion.

2.4 Administration Instructions

ZULRESSO must be diluted before administration [see Dosage and Administration (2.3)]. The following are important administration instructions:

• Use a programmable peristaltic infusion pump to ensure accurate delivery of ZULRESSO.

• Administer ZULRESSO via a dedicated line. Do not inject other medications into the infusion bag or mix with ZULRESSO.
- Fully prime infusion administration sets with admixture before inserting into the pump and connecting to the venous catheter.
- Use a PVC, non-DEHP, nonlatex infusion set. Do not use in-line filter infusion sets.

2.5 Recommendations in Patients with End Stage Renal Disease
Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 m² because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium [see Clinical Pharmacology (12.3, 12.6)].

3 DOSAGE FORMS AND STRENGTHS
Injection: 100 mg/20 mL (5 mg/mL) clear, colorless solution in a single-dose vial.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Excessive Sedation and Sudden Loss of Consciousness
In clinical studies, ZULRESSO caused sedation and somnolence that required dose interruption or reduction in some patients during the infusion (5% of ZULRESSO-treated patients compared to 0% of placebo-treated patients). Some patients 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). Time to full recovery from loss or altered state of consciousness, after dose interruption, ranged from 15 to 60 minutes. 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). All patients with loss of or altered state of consciousness recovered with dose interruption.

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.

During the infusion, monitor patients for sedative effects every 2 hours during planned, non-sleep periods. 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 [see Dosage and Administration (2.2)].

Immediately stop the infusion if pulse oximetry reveals hypoxia. After hypoxia, the infusion should not be resumed.
Patients should be cautioned against engaging in potentially hazardous activities requiring mental alertness, such as driving after infusion until any sedative effects of ZULRESSO have dissipated. Patients must be accompanied during interactions with their child(ren) while receiving the infusion because of the potential for excessive sedation and sudden loss of consciousness.

Concomitant use of opioids, antidepressants, or other CNS depressants such as benzodiazepines or alcohol may increase the likelihood or severity of adverse reactions related to sedation [see Drug Interactions (7.1, 7.2)].

Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the ZULRESSO REMS [see Warnings and Precautions (5.2)].

5.2 ZULRESSO Risk Evaluation and Mitigation Strategy (REMS)

ZULRESSO is available only through a restricted program under a REMS called the ZULRESSO REMS because excessive sedation or sudden loss of consciousness can result in serious harm [see Warnings and Precautions (5.1)].

Notable requirements of the ZULRESSO REMS include the following:

- Healthcare facilities must enroll in the program and ensure that ZULRESSO is only administered to patients who are enrolled in the ZULRESSO REMS.
- Pharmacies must be certified with the program and must only dispense ZULRESSO to healthcare facilities who are certified in the ZULRESSO REMS.
- Patients must be enrolled in the ZULRESSO REMS prior to administration of ZULRESSO.
- Wholesalers and distributors must be registered with the program and must only distribute to certified healthcare facilities and pharmacies.

Further information, including a list of certified healthcare facilities, is available at www.zulressorems.com or 1-844-472-4379.

5.3 Suicidal Thoughts and Behaviors

In pooled analyses of placebo-controlled trials of chronically administered antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with major depressive disorder (MDD). The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.
Table 1: Risk Differences of the Number of Patients with Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

<table>
<thead>
<tr>
<th>Age Range (years)</th>
<th>Drug-Placebo Difference in Number of Patients with Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>&lt;18</td>
<td>14 additional patients</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional patients</td>
</tr>
<tr>
<td></td>
<td>Decreases Compared to Placebo</td>
</tr>
<tr>
<td>25-64</td>
<td>1 fewer patient</td>
</tr>
</tbody>
</table>

*ZULRESSO is not approved in pediatric patients.

ZULRESSO does not directly affect monoaminergic systems. Because of this and the comparatively low number of exposures to ZULRESSO, the risk of developing suicidal thoughts and behaviors with ZULRESSO is unknown. Consider changing the therapeutic regimen, including discontinuing ZULRESSO, in patients whose depression becomes worse or who experience emergent suicidal thoughts and behaviors.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Excessive Sedation and Sudden Loss of Consciousness [see Boxed Warning, Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data described below reflect exposure to ZULRESSO in 140 patients with postpartum depression (PPD). A titration to a target dosage of 90 mcg/kg/hour was evaluated in 102 patients and a titration to a target dose of 60 mcg/kg/hour was evaluated in 38 patients [see Clinical Studies (14)]. Patients were then followed for 4 weeks.

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush (Table 2).

Adverse Reactions Leading to Discontinuation, Dosage Interruption, or Dosage Reduction

In the pooled placebo controlled-studies, the incidence of patients who discontinued due to any adverse reaction was 2% of ZULRESSO-treated patients compared to 1% of placebo-treated patients. The adverse reactions leading to treatment discontinuation in ZULRESSO-treated
patients were sedation-related (loss of consciousness, vertigo, syncope, and presyncope) or infusion site pain.

In the pooled placebo controlled-studies, the incidence of patients who had an interruption or reduction of the dosage due to any adverse reaction was 7% of ZULRESSO-treated patients compared to 3% of placebo-treated patients. The adverse reactions leading to dose reduction or interruption in ZULRESSO-treated patients were sedation-related (loss of consciousness, syncope, somnolence, dizziness, fatigue), infusion site events, changes in blood pressure, or medication error due to infusion pump malfunction. 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.

Table 2 presents the adverse reactions that occurred in ZULRESSO-treated PPD patients at a rate of at least 2% and at a higher rate than in the placebo-treated patients during the 60-hour treatment period.
Table 2: Adverse Reactions in Placebo-Controlled Studies in Patients with PPD Reported in ≥2% of ZULRESSO-Treated Patients and Greater than Placebo-Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=107)</th>
<th>Maximum dosage 60 mcg/kg/hour (n=38)</th>
<th>Maximum dosage 90 mcg/kg/hour (Recommended dosage) (n=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiac Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>-</td>
<td>-</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>-</td>
<td>-</td>
<td>2%</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>-</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness, presyncope, vertigo</td>
<td>7%</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Loss of consciousness</td>
<td>-</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Sedation, somnolence</td>
<td>6%</td>
<td>21%</td>
<td>13%</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flushing, hot flush</td>
<td>-</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

7 DRUG INTERACTIONS

7.1 CNS Depressants
Concomitant use of ZULRESSO with CNS depressants (e.g., opioids, benzodiazepines) may increase the likelihood or severity of adverse reactions related to sedation [see Warnings and Precautions (5.1)].

7.2 Antidepressants
In the placebo-controlled studies, a higher percentage of ZULRESSO-treated patients who used concomitant antidepressants reported sedation-related events [see Warnings and Precautions (5.1)].
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at [https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/](https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/).

Risk Summary

Based on findings from animal studies of other drugs that enhance GABAergic inhibition, ZULRESSO may cause fetal harm. There are no available data on ZULRESSO use in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal reproduction studies, malformations were not seen in rats or rabbits at plasma levels up to 5 and 6 times the maximum recommended human dose (MRHD), respectively. Developmental toxicities were seen in the fetuses of rats and rabbits at 5 and ≥3 times the plasma levels at the MRHD, respectively. Reproductive toxicities were seen in rabbits at ≥3 times the plasma levels at the MRHD. These effects were not seen in rats and rabbits at 2 and 1.2 times the plasma levels at the MRHD. Brexanolone administered to pregnant rats during pregnancy and lactation resulted in lower pup survival at doses which were associated with ≥2 times the plasma levels at the MRHD and a neurobehavioral deficit in female offspring at 5 times the plasma levels at the MRHD. These effects were not seen at 0.8 times and 2 times the plasma levels at the MRHD, respectively (see Data).

In published animal studies, administration of other drugs that enhance GABAergic inhibition to neonatal rats caused widespread apoptotic neurodegeneration in the developing brain. The window of vulnerability to these changes in rats (postnatal days 0-14) corresponds to the period of brain development that takes place during the third trimester of pregnancy in humans.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

In pregnant rats and rabbits, no malformations were seen when brexanolone was given during the period of organogenesis at continuous intravenous doses up to 60 and 30 mg/kg/day, respectively. These doses were associated with maternal plasma levels 5 and 6 times the plasma levels at the MRHD of 90 mcg/kg/hour, in rats and rabbits, respectively. In rats, a decrease in fetal body weights was seen at 60 mg/kg/day (5 times the plasma level at the MRHD). In rabbits, increased numbers of late resorptions and a decrease in fetal body weights were seen at doses equal to and greater than 15 mg/kg/day (3 times the plasma levels at the MRHD) with fewer live
fetuses and a higher post implantation loss seen at 30 mg/kg/day (6 times the plasma levels at the MRHD) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain and/or body weight loss). Effects in rats and rabbits were not seen at 2 and 1.2 times the plasma levels at the MRHD, respectively.

When brexanolone was administered to pregnant rats by continuous intravenous administration at 30 and 60 mg/kg/day (2 and 5 times plasma levels at the MRHD, respectively) during the period of organogenesis and throughout pregnancy and lactation, increased numbers of dead pups and fewer live pups at birth were seen. This effect was not seen at 0.8 times the plasma levels at the MRHD. Decreased pup viability between postnatal day 0 and 4 in the presence of maternal toxicity (decreased body weight gain and food consumption during lactation) was seen at 5 times the plasma levels at the MRHD. These effects were not seen at 2 times the plasma levels at the MRHD. A neurobehavioral deficit, characterized by slower habituation in the maximal startle response in the auditory startle test, was seen in female offspring of dams dosed at 5 times the plasma levels at the MRHD. This effect was not seen at 2 times the plasma levels at the MRHD.

8.2 **Lactation**

**Risk Summary**

Available data from a lactation study in 12 women indicate that brexanolone is transferred to breastmilk in nursing mothers. However, the relative infant dose (RID) is low, 1% to 2% of the maternal weight-adjusted dosage (see Data). Also, as ZULRESSO has low oral bioavailability (<5%) in adults, infant exposure is expected to be low. There were no reports of effects of ZULRESSO on milk production. There are no data on the effects of ZULRESSO on a breastfed infant. Available data on the use of ZULRESSO during lactation do not suggest a significant risk of adverse reactions to breastfed infants from exposure to ZULRESSO. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for ZULRESSO and any potential adverse effects on the breastfed child from ZULRESSO or from the underlying maternal condition.

**Data**

A study was conducted in twelve healthy adult lactating women treated with intravenous ZULRESSO according to the recommended 60-hour dosing regimen (maximum dosage was 90 mcg/kg/hour). Concentrations of ZULRESSO in breast milk were at low levels (<10 ng/mL) in >95% of women by 36 hours after the end of the infusion of ZULRESSO. The calculated maximum relative infant dose for ZULRESSO during the infusion was 1% to 2%.

8.4 **Pediatric Use**

The safety and effectiveness of ZULRESSO in pediatric patients have not been established.

8.5 **Geriatric Use**

PPD is a condition associated with pregnancy; there is no geriatric experience with ZULRESSO.
8.6 Hepatic Impairment
Dosage adjustment in patients with hepatic impairment is not necessary. Modest increases in exposure to unbound brexanolone and modest decreases in exposure to total brexanolone were observed in patients with moderate to severe hepatic impairment (Child-Pugh ≥7) with no associated change in tolerability [see Clinical Pharmacology (12.3)].

8.7 Renal Impairment
No dosage adjustment is recommended in patients with mild (eGFR 60 to 89 mL/minute/1.73 m²), moderate (eGFR 30 to 59 mL/minute/1.73 m²) or severe (eGFR 15 to 29 mL/minute/1.73 m²) renal impairment [see Clinical Pharmacology (12.3)].

Avoid use of ZULRESSO in patients with end stage renal disease (ESRD) with eGFR of < 15 mL/minute/1.73 m² because of the potential accumulation of the solubilizing agent, betadex sulfobutyl ether sodium [see Clinical Pharmacology (12.3, 12.6)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance
ZULRESSO contains brexanolone, a Schedule IV controlled substance under the Controlled Substances Act.

9.2 Abuse
In a human abuse potential study, 90 mcg/kg, 180 mcg/kg (two times the maximum recommended infusion rate), and 270 mcg/kg (three times the maximum recommended infusion rate) ZULRESSO infusions over a one-hour period were compared to oral alprazolam administration (1.5 mg and 3 mg). On positive subjective measures of “drug liking”, “overall drug liking”, “high” and “good drug effects”, the 90 mcg/kg dosage produced scores that were similar to placebo. Scores on these positive subjective measures for both dosages of ZULRESSO 90 mcg/kg and 180 mcg/kg were lower than both alprazolam doses. However, the scores on the positive subjective measures for ZULRESSO 270 mcg/kg dosage were similar to those produced by both doses of alprazolam. In this study, 3% of subjects administered ZULRESSO 90 mcg/kg and 13% administered ZULRESSO 270 mcg/kg reported euphoric mood, compared to none administered placebo during the one-hour administration.

9.3 Dependence
In the PPD clinical studies conducted with ZULRESSO, end of treatment occurred through tapering. Thus, in these studies it was not possible to assess whether abrupt discontinuation of ZULRESSO produced withdrawal symptoms indicative of physical dependence. It is recommended that ZULRESSO be tapered according to the dosage recommendations, unless symptoms warrant immediate discontinuation [see Dosage and Administration (2.2), Warnings and Precautions (5.1)].
10 OVERDOSAGE

Human Experience

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 [see Warnings and Precautions (5.1)] and the potential for accompanying respiratory changes.

Management of Overdose

In case of overdosage, stop the infusion immediately and initiate supportive measures as necessary. Brexanolone is rapidly cleared from plasma [see Clinical Pharmacology (12.3)]. Consult a Certified Poison Control Center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION

ZULRESSO contains brexanolone, a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator, that is chemically identical to endogenous allopregnanolone.

The molecular formula of brexanolone is C21H34O2. The relative molecular mass is 318.5 Da. The chemical structure is:

![Chemical Structure](image)

ZULRESSO (brexanolone) injection is a sterile, clear, colorless, and preservative-free solution. ZULRESSO 5 mg/mL is hypertonic and must be diluted prior to administration as an intravenous infusion [see Dosage and Administration (2.3)]. Each mL of solution contains 5 mg of brexanolone, 250 mg of betadex sulfobutyl ether sodium, 0.265 mg of citric acid monohydrate, 2.57 mg of sodium citrate dihydrate, and water for injection. Hydrochloric acid or sodium hydroxide may be used during manufacturing to adjust pH.
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
The mechanism of action of brexanolone in the treatment of PPD in adults is not fully understood, but is thought to be related to its positive allosteric modulation of GABA<sub>α</sub> receptors.

12.2 Pharmacodynamics
Brexanolone potentiated GABA-mediated currents from recombinant human GABA<sub>α</sub> receptors in mammalian cells expressing α<sub>1</sub>β<sub>2</sub>γ<sub>2</sub> receptor subunits, α<sub>4</sub>β<sub>3</sub>δ receptor subunits, and α<sub>6</sub>β<sub>3</sub>δ receptor subunits.

Brexanolone exposure-response relationships and the time course of pharmacodynamics response are unknown.

Cardiac Electrophysiology
The effect of brexanolone on the QT interval was evaluated in a Phase 1 randomized, placebo and positive controlled, double-blind, three-period crossover thorough QT study in 30 healthy adult subjects. At 1.9-times the exposure occurring at the highest recommended infusion rate (90 mcg/kg/hour), brexanolone did not prolong the QT interval to a clinically relevant extent.

12.3 Pharmacokinetics
Brexanolone exhibited dose proportional pharmacokinetics over a dosage range of 30 mcg/kg/hour to 270 mcg/kg/hour (three times the maximum recommended dosage). Mean steady state exposure at 60 mcg/kg/hour and 90 mcg/kg/hour was around 52 ng/mL and 79 ng/mL, respectively.

Distribution
The volume of distribution of brexanolone was approximately 3 L/kg, suggesting extensive distribution into tissues. Plasma protein binding was greater than 99% and is independent of plasma concentrations.

Elimination
The terminal half-life of brexanolone is approximately 9 hours. The total plasma clearance of brexanolone is approximately 1 L/h/kg.

Metabolism
Brexanolone is extensively metabolized by non-CYP based pathways via three main routes - keto-reduction (AKRs), glucuronidation (UGTs), and sulfation (SULTs). There are three major circulating metabolites that are pharmacologically inactive and do not contribute to the overall efficacy of ZULRESSO.

Excretion
Following administration of radiolabeled brexanolone, 47% was recovered in feces (primarily as metabolites) and 42% in urine (with less than 1% as unchanged brexanolone).
Specific Populations
No clinically significant differences in the pharmacokinetics of brexanolone were observed based on renal impairment (severe) study or hepatic impairment (mild, moderate, severe) study. The effect of end stage renal disease (ESRD, eGFR < 15 mL/minute/1.73 m²) on brexanolone pharmacokinetics is unknown. However, avoid use of ZULRESSO in patients with ESRD [see Use in Specific Populations (8.7)].

Drug Interaction Studies
No studies were conducted to evaluate the effects of other drugs on ZULRESSO.

No clinically significant differences in the pharmacokinetics of phenytoin (CYP2C9 substrate) were observed when it was used concomitantly with brexanolone.

12.6   Betadex Sulfobutyl Ether Sodium Pharmacokinetics
Betadex sulfobutyl ether sodium is a solubilizing agent in ZULRESSO. In patients with severe renal impairment (eGFR 15-29 mL/minute/1.73 m²), betadex sulfobutyl ether sodium AUC_{inf} increased 5.5-fold and C_{max} increased 1.7-fold. Avoid use of ZULRESSO in patients with ESRD [see Use in Specific Populations (8.7)].

13   NONCLINICAL TOXICOLOGY
13.1   Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis
Carcinogenicity studies of brexanolone have not been performed.

Mutagenesis
Brexanolone was not genotoxic when tested in an in vitro microbial mutagenicity (Ames) assay, an in vitro micronucleus assay in human peripheral blood lymphocytes, and an in vivo rat bone marrow micronucleus assay.

Impairment of Fertility
Treatment of female and male rats with brexanolone at doses equal to and greater than 30 mg/kg/day, which is associated with 2 times the plasma levels at the maximum recommended human dose (MRHD) of 90 mcg/kg/hour, caused impairment of female and male fertility and reproduction. In female rats, brexanolone was associated with decreased mating and fertility indices, an increase in number of days to mating, prolonged/irregular estrous cycles, an increase in the number of early resorptions, and post implantation loss. Reversal of effects in females was observed following a 28-day recovery period. In male rats, brexanolone was associated with decreased mating and fertility indices, decreased conception rate, lower prostate, seminal vesicle, and epididymis weight, as well as decreased sperm numbers. Impaired female and male fertility and reproduction were not observed at 0.8 times the MRHD.
The efficacy of ZULRESSO in the treatment of postpartum depression (PPD) was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies (referred to as Studies 1 and 2) in women (18 to 45 years) with PPD who met the Diagnostic and Statistical Manual of Mental Disorders criteria for a major depressive episode (DSM-IV) with onset of symptoms in the third trimester or within 4 weeks of delivery. In these studies, patients received a 60-hour continuous intravenous infusion of ZULRESSO or placebo and were then followed for 4 weeks. Study 1 (NCT02942004) included patients with severe PPD (Hamilton Depression Rating Scale (HAM-D) score ≥ 26), and Study 2 (NCT02942017) included patients with moderate PPD (HAM-D score of 20 to 25). A titration to the recommended target dosage of 90 mcg/kg/hour was evaluated in both studies (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 20 hours, 90 mcg/kg/hour for 28 hours, followed by a taper to 60 mcg/kg/hour for 4 hours and then 30 mcg/kg/hour for 4 hours). A titration to a target dosage of 60 mcg/kg/hour (patients received 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 52 hours, then 30 mcg/kg/hour for 4 hours) was also evaluated in Study 1.

Demographic and baseline disease characteristics were generally similar across treatment groups in the pooled Studies 1 and 2. Most patients were White (63%) or Black (34%); 18% of patients identified as Hispanic or Latina; the average age of women receiving ZULRESSO was 28 years. Most patients (76%) had onset of PPD symptoms within 4 weeks after delivery, with the remainder having onset during the third trimester. Baseline oral antidepressant use was reported for 23% of patients.

The primary endpoint was the mean change from baseline in depressive symptoms as measured by the HAM-D total score at the end of the infusion (Hour 60). A pre-specified secondary efficacy endpoint was the mean change from baseline in HAM-D total score at Day 30. In both placebo-controlled studies, titration to a target dose of ZULRESSO 90 mcg/kg/hour was superior to placebo in improvement of depressive symptoms. In a group of 38 patients in Study 1, a ZULRESSO titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms.
<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group (# ITT subject)</th>
<th>Primary Endpoint: Change from Baseline in HAM-D Total Score at Hour 60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean Baseline Score (SD)</td>
</tr>
<tr>
<td>1</td>
<td>ZULRESSO target dosage 90 mcg/kg/hour (n=41)*</td>
<td>28.4 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=43)</td>
<td>28.6 (2.5)</td>
</tr>
<tr>
<td></td>
<td>ZULRESSO target dosage 60 mcg/kg/hour (n=38)*</td>
<td>29.0 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=43)</td>
<td>28.6 (2.5)</td>
</tr>
<tr>
<td>2</td>
<td>ZULRESSO target dosage 90 mcg/kg/hour (n=51)*</td>
<td>22.6 (1.6)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n=53)</td>
<td>22.7 (1.6)</td>
</tr>
</tbody>
</table>

HAM-D: Hamilton depression rating scale; ITT: intention to treat; SD: standard deviation; LS: least squares; SE: standard error; CI: confidence interval; *: statistically significant after multiplicity adjustments.

Examination of subgroups by race did not suggest differences in response.

**Time Course of Treatment Response**

*Figure 1* shows the time course of response for the ZULRESSO 90 mcg/kg/hour-target and 60 mcg/kg/hour-target groups compared to the placebo group for Study 1.
Figure 1: Change from Baseline in HAM-D Total Score Over Time (Days) in Study 1

*ZULRESSO was administered via a 60-hour intravenous infusion as follows:

90 mcg/kg/hour-target dosage: 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 20 hours, 90 mcg/kg/hour for 28 hours, 60 mcg/kg/hour for 4 hours, 30 mcg/kg/hour for 4 hours

60 mcg/kg/hour-target dosage: 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 52 hours, 30 mcg/kg/hour for 4 hours

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ZULRESSO injection is supplied as 100 mg brexanolone in 20 mL (5 mg/mL) single-dose vials containing a sterile, preservative-free, clear, colorless solution. NDC 72152-547-20
Storage and Handling
Store the undiluted ZULRESSO product at 2°C to 8°C (36°F to 46°F). Do not freeze. Store protected from light.
The diluted product in the infusion bag can be used at room temperature for up to 12 hours. If the diluted product is not used immediately after dilution, store under refrigerated conditions for up to 96 hours [see Dosage and Administration (2.3)].

17  PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Excessive Sedation and Sudden Loss of Consciousness
Patients may experience loss of consciousness or altered state of consciousness during the ZULRESSO infusion. Advise patients to report signs of excessive sedation that may occur during the infusion. Patients must not be the primary caregiver of dependents and must be accompanied during interactions with their child(ren) [see Warnings and Precautions (5.1)].

ZULRESSO Risk Evaluation and Mitigation Strategy (REMS)
ZULRESSO is available only through a restricted program called the ZULRESSO REMS [see Warnings and Precautions (5.2)].
Inform the patient of the following notable requirements:

• Patients must be enrolled in the ZULRESSO REMS Program prior to administration.
• Patients must be monitored during administration of ZULRESSO and report any signs and symptoms of excessive sedation to a healthcare provider.

Potential for Abuse
Advise patients that ZULRESSO can be abused or lead to dependence [see Drug Abuse and Dependence (9)].

Concomitant Medications
Caution patients that opioids or other CNS depressants, such as benzodiazepines, taken in combination with ZULRESSO may increase the severity of sedative effects [see Warnings and Precautions (5.1, 5.2), Drug Interactions (7.1)].

Suicide Thoughts and Behaviors
Advise patients and caregivers to look for the emergence of suicidal thoughts and behavior and instruct them to report such symptoms to the healthcare provider [see Warnings and Precautions (5.3)].

Pregnancy
Advise women to notify their healthcare provider if they could possibly be pregnant prior to therapy with ZULRESSO. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise patients that there is a pregnancy exposure registry that monitors
pregnancy outcomes in women exposed to ZULRESSO during pregnancy [see Use in Specific Populations (8.1)].

Manufactured for:
Sage Therapeutics, Inc.,
Cambridge, MA 02142 USA

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What is the most important information I should know about ZULRESSO?

ZULRESSO can cause serious side effects, including:

- Excessive sedation and sudden loss of consciousness. ZULRESSO may cause you to feel very sleepy (excessive sedation) or pass out (loss of consciousness). Your healthcare provider should check you for symptoms of excessive sleepiness every 2 hours while you are awake.
  
  o During your ZULRESSO infusion, tell your healthcare provider right away if you feel like you cannot stay awake during the time you are normally awake or if you feel like you are going to pass out. Your healthcare provider may lower your dose or stop the infusion until your symptoms go away.
  
  o You must have a caregiver or family member with you to help care for your child(ren) during your ZULRESSO infusion.
- Because of the risk of serious harm resulting from excessive sedation or sudden loss of consciousness, ZULRESSO is only available through a restricted program called the ZULRESSO REMS.

What is ZULRESSO?

ZULRESSO is a prescription medicine used in adults to treat a certain type of depression called Postpartum Depression.

Before receiving ZULRESSO, tell your healthcare provider about all your medical conditions, including if you:

- drink alcohol
- have kidney problems
- are pregnant or think you may be pregnant. It is not known if ZULRESSO will harm your unborn baby.
  
  o There is a pregnancy registry for females who are exposed to ZULRESSO during pregnancy. The purpose of the registry is to collect information about the health of females exposed to ZULRESSO and their baby. If you become pregnant during treatment with ZULRESSO, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visit https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/
- are breastfeeding or plan to breastfeed. ZULRESSO passes into breast milk. Talk to your healthcare provider about the risks and benefits of breastfeeding and about the best way to feed your baby while receiving ZULRESSO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ZULRESSO and some medicines may interact with each other and cause serious side effects.

Especially tell your healthcare provider if you take:

- other antidepressants
- opioids
- CNS depressants such as benzodiazepines

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine. Your healthcare provider will decide if other medicines can be taken with ZULRESSO.

How will I receive ZULRESSO?

- ZULRESSO is given to you by continuous intravenous (IV) infusion into your vein. Your ZULRESSO infusion will last for a total of 60 hours (2.5 days).

What should I avoid while receiving ZULRESSO?

- ZULRESSO may make you feel dizzy and sleepy. Do not drive a car or do other dangerous activities after your ZULRESSO infusion until your feeling of sleepiness has completely gone away. See “What is the most important information I should know about ZULRESSO?”
- Do not drink alcohol while receiving ZULRESSO.
What are the possible side effects of ZULRESSO?

ZULRESSO can cause serious side effects, including:

- See “What is the most important information I should know about ZULRESSO?”
- Increased risk of suicidal thoughts or actions. ZULRESSO and other antidepressant medicines may increase suicidal thoughts and actions in some people 24 years of age and younger. Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions.

How can I watch for and try to prevent suicidal thoughts and actions?

- Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
- Tell your healthcare provider right away if you have any new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Tell your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- attempts to commit suicide
- thoughts about suicide or dying
- new or worse depression
- other unusual changes in behavior or mood

The most common side effects of ZULRESSO include:

- sleepiness
- dry mouth
- passing out
- flushing of the skin or face

These are not all the side effects of ZULRESSO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about ZULRESSO.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your healthcare provider for information about ZULRESSO that is written for health professionals.

What are the ingredients in ZULRESSO?

Active ingredient: brexanolone

Inactive ingredients: betadex sulfobutyl ether sodium, citric acid monohydrate, sodium citrate dihydrate, and water for injection. Hydrochloric acid or sodium hydroxide may be added during manufacturing to adjust pH.

Manufactured for:
Sage Therapeutics, Inc.,
Cambridge, MA 02142

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For more information about ZULRESSO go to www.zulresso.com or call 844-472-4379.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: June 2019