



brexanolone (Zulresso™)

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider brexanolone (Zulresso™)[‡] for the treatment of postpartum depression to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for brexanolone (Zulresso) will be considered when the following criteria are met:

- I. Patient is ≥ 15 years of age; AND
- II. Patient has a diagnosis of moderate to severe postpartum depression; AND meets ONE of the following (a or b):
 - a. Hamilton Rating Scale for Depression (HAM-D) score ≥ 20 ; OR
 - b. Edinburgh Postnatal Depression Scale (EPDS) score ≥ 13 ; AND

*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- III. Onset of major depressive episode between 3rd trimester through 4 weeks postpartum; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- IV. Patient will be ≤ 6 months postpartum at the time of infusion; AND
*(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)*
- V. ONE of the following (a or b) is present:
 - a. Patient has recurrent thoughts of death, suicidal ideation, or attempt; OR

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

brexanolone (Zulresso™)

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

- b. Patient meets the following criteria (i, ii, iii, iv, AND v) for diagnosis of a major depressive disorder episode (DSM-5 criteria):
 - i. Presence of 5 or more of the following symptoms for at least 2 weeks (one of which must be either depressed mood or anhedonia):
 - 1. Depressed mood most of the day nearly every day
 - 2. Anhedonia most of the day nearly every day
 - 3. Significant weight loss or gain
 - 4. Insomnia or hypersomnia
 - 5. Psychomotor agitation or retardation
 - 6. Fatigue or loss of energy
 - 7. Feelings of worthlessness or excessive guilt
 - 8. Diminished ability to think or concentrate; indecisiveness
 - 9. Recurrent thoughts of death; suicidal ideation or attempt; AND
 - ii. Symptoms cause clinically significant distress or functional impairment; AND
 - iii. Episode is not attributable to the physiologic effects of a substance or another medical condition; AND
 - iv. Episode is not better explained by a psychotic illness; AND
 - v. There has never been a manic or hypomanic episode; AND
- VI. Patient is not currently pregnant; AND
- VII. Zulresso will only be administered one time per postpartum period.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of brexanolone (Zulresso) when the patient does not have a HAM-D or EPDS score confirming moderate to severe depression, the depressive episode did not begin in the peripartum period, or the patient is >6 months postpartum, to be **not medically necessary**.**

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

brexanolone (Zulresso™)

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of brexanolone (Zulresso) when patient selection criteria are not met (except those denoted as **not medically necessary****) to be **investigational.***

Based on review of available data, the Company considers the use of brexanolone (Zulresso) for indications other than postpartum depression to be **investigational.***

Policy Guidelines

Depression Scales

Hamilton Rating Scale for Depression (HAM-D)

HAM-D is a 17-item rating scale to determine the severity level of depression in a patient before, during, and after treatment. The total score ranges from 0 to 52, with the score corresponding to the following classifications:

- 0-7: No depression (normal)
- 8-16: Mild depression
- 17-23: Moderate depression
- ≥ 24 : Severe depression

Edinburgh Postnatal Depression Scale (EPDS)

EPDS is a self-report instrument containing ten items that are ranked from 0 to 3 that reflect the patient's experience over the past week. The total score ranges from 0 to 30. An EPDS ≥ 13 is an acceptable cut-point for identifying women at risk for major depression in clinical settings.

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

brexanolone (Zulresso™)

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

Diagnostic Criteria for a Major Depressive Episode

Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

A	Five or more symptoms for 2 weeks (one of which must be either depressed mood or anhedonia)	<ol style="list-style-type: none">1. Depressed mood most of the day nearly every day2. Anhedonia most of the day nearly every day3. Significant weight loss or gain4. Insomnia or hypersomnia5. Psychomotor agitation or retardation6. Fatigue or loss of energy7. Feelings of worthlessness or excessive guilt8. Diminished ability to think or concentrate; indecisiveness9. Recurrent thoughts of death; suicidal ideation or attempt
B	Symptoms cause clinically significant distress or functional impairment	
C	The episode is not attributable to the physiological effects of a substance or another medical condition	
D	The episode is not better explained by a psychotic illness	
E	There has never been a manic or hypomanic episode	

Background/Overview

Zulresso is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator and is the first drug to be approved specifically for the treatment of postpartum depression. While the mechanism of action is not fully understood, it is known that the active ingredient of Zulresso, brexanolone, is chemically identical to endogenous allopregnanolone, a chemical that increases in the plasma during pregnancy and decreases substantially after childbirth in humans. Fluctuations in allopregnanolone have demonstrated effects on anxiety and depression in animal models. Zulresso should be administered as a continuous intravenous (IV) infusion over 60 hours with titration following a schedule listed in the FDA-approved package insert. Due to the risk of excessive

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



brexanolone (Zulresso[™])

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

sedation and sudden loss of consciousness, Zulresso is available only through a restricted distribution system under a Risk Evaluation and Mitigation Strategy (REMS). Healthcare facilities and patients must be enrolled in the program and pharmacies must be certified with the program. A healthcare provider must be available on site to continuously monitor the patient for the duration of the Zulresso infusion.

Postpartum depression is a major depressive episode with onset during pregnancy or within 4 weeks of delivery that can have serious effects on the maternal-infant bond and later infant development. In the United States, postpartum depression has an overall prevalence of approximately 12%. It is symptomatically indistinguishable from major depression, but the timing of its onset has led to the acknowledgement of it potentially being a unique illness. As with other forms of depression, it is characterized by sadness and/or loss of interest in activities that one used to enjoy and a decreased ability to feel pleasure and may present with symptoms such as cognitive impairment, feelings of worthlessness or guilt, or suicidal ideation. Because of the risk of suicide, postpartum depression is considered a life-threatening condition.

Zulresso is the first and only FDA-approved medication for the treatment of postpartum depression. No other antidepressants are indicated for postpartum depression, and data on their effectiveness are limited. Non-drug treatments such as electroconvulsive shock therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and psychotherapy have been used to treat postpartum depression. Antidepressant medications are the most common treatments for depression in general and among postpartum women with moderate to severe depression. However, many women prefer not to take antidepressants during pregnancy or the postpartum period when they are breastfeeding. There is not strong evidence demonstrating that the amount of medication in the breastmilk is sufficient to cause harm to the infant, but many women choose to avoid even a small potential risk. Due to their short half-lives, the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine are the recommended initial oral antidepressant therapy for nursing women unless the woman has a history of efficacy with a different antidepressant.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Zulresso was approved in 2019 for the treatment of postpartum depression in adults. In June 2022, the label was expanded to include patients aged 15-17 years.

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

brexanolone (Zulresso™)

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Zulresso in the treatment of postpartum depression (PPD) was demonstrated in two multicenter, randomized, double-blind, placebo-controlled studies in women with PPD who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a major depressive episode with onset of symptoms in the third trimester or within 4 weeks of delivery. In both studies, patients received a 60 hour continuous intravenous infusion of Zulresso or placebo and were then followed for 4 weeks. Study 1 included patients with severe PPD (Hamilton Depression Rating Scale [HAM-D] score ≥ 26), and Study 2 included patients with moderate PPD (HAM-D score of 20 to 25). A titration to the recommended target dosage of 90 mcg/kg/hr was evaluated in both studies. A titration to a target dosage of 60 mcg/kg/hr was also evaluated in Study 1. 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). In both studies, titration to a target dose of Zulresso 90 mcg/kg/hr was superior to placebo in improvement of depressive symptoms. In study 1, patients had a least squares mean change from baseline in HAM-D total score of -17.7 in the Zulresso 90 mcg/kg/hr group versus a -14.0 change in the placebo group ($p=0.0252$). In study 2, patients had a least squares mean change from baseline in HAM-D total score of -14.6 in the Zulresso group versus a -12.1 change in the placebo group ($p=0.016$).

Zulresso pharmacokinetics were evaluated in 20 patients aged 15-17 years with PPD and were comparable to those in adult patients with PPD. Additionally, safety in this age group was evaluated in an open-label study of 20 patients with PPD who were then followed for 4 weeks. Adverse reactions were generally similar to those observed in clinical studies of Zulresso in adults with PPD.

References

1. Zulresso [package insert]. Sage Therapeutics. Cambridge, MA. Updated June 2022.
2. Zulresso Drug Evaluation. Express Scripts. Updated April 2019.

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

brexanolone (Zulresso™)

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

Policy History

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

09/03/2019 Medical Policy Committee review

09/11/2019 Medical Policy Implementation Committee approval. New policy.

12/11/2019 Coding update

09/03/2020 Medical Policy Committee review

09/09/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

09/02/2021 Medical Policy Committee review

09/08/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged. Added an investigational statement for clarity for the use of brexanolone (Zulresso) for indications other than postpartum depression.

08/04/2022 Medical Policy Committee review

08/10/2022 Medical Policy Implementation Committee approval. Updated age requirement to reflect new FDA approved age.

08/03/2023 Medical Policy Committee review

08/09/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 08/2024

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2022 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units,

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



brexanolone (Zulresso™)

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1632
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



brexanolone (Zulresso[™])

Policy # 00685

Original Effective Date: 09/11/2019

Current Effective Date: 09/11/2023

3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2023 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.