RXADVANCE
2 Park Central Drive
Southborough, MA 01772

Clinical Policy Title:	brexanolone
Policy Number:	RxA.579
Drug(s) Applied:	Zulresso®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

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

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
brexanolone (Zulresso®)	PPD	Administered as a continuous intravenous infusion over 60 hours (2.5 days) as follows: • 0 to 4 hours: Initiate with a dosage of 30 mcg/kg per hour • 4 to 24 hours: Increase dosage to 60 mcg/kg per hour • 24 to 52 hours: Increase dosage to 90 mcg/kg per hour (alternatively consider a dosage of 60 mcg/kg per hour for those who do not tolerate 90 mcg/kg per hour) • 52 to 56 hours: Decrease dosage to 60 mcg/kg per hour • 56 to 60 hours: Decrease dosage to 30 mcg/kg per hour	90 mcg/kg per hour

Dosage Forms

- Vial for injection, single-dose: 100 mg/20 mL (5 mg/mL)

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

I. Initial Approval Criteria

A. Postpartum Depression (must meet all):

1. Diagnosis of major depressive disorder with postpartum onset based on DSM-IV criteria, defined as a

major depressive episode with onset in the third trimester or within 4 weeks of delivery;
2. Prescribed by or in consultation with psychiatrist;
3. Age 18 years of age or older;
4. Documentation of HAM-D score range, PHQ-9 score, or MADRS score range indicating moderate to severe PPD (*see Appendix D*);
5. Failure of an 8-week trial of one of the following oral antidepressants at up to the maximally indicated dose but no less than the commonly recognized minimum therapeutic dose, unless contraindicated or clinically significant adverse effects are experienced: selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressant (TCA), bupropion, mirtazapine (*see Appendix B*);
6. No more than 6 months have passed since member has given birth;
7. Dose does not exceed 90 mcg/kg per hour over 60 hours (2.5 days) as follows:
   a. 0 to 4 hours: Initiate with a dosage of 30 mcg/kg per hour;
   b. 4 to 24 hours: Increase dosage to 60 mcg/kg per hour;
   c. 24 to 52 hours: Increase dosage to 90 mcg/kg per hour (alternatively consider a dosage of 60 mcg/kg per hour for those who do not tolerate 90 mcg/kg per hour);
   d. 52 to 56 hours: Decrease dosage to 60 mcg/kg per hour;
   e. 56 to 60 hours: Decrease dosage to 30 mcg/kg per hour.

Approval Duration
Commercial: 30 days (one-time infusion per pregnancy)
Medicaid: 30 days (one-time infusion per pregnancy)

II. Continued Therapy Approval

A. Postpartum Depression

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

Approval Duration
Commercial: Not applicable
Medicaid: Not applicable

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
HAM-D: Hamilton Rating Scale for Depression
MADRS: Montgomery-Åsberg Depression Rating Scale
PHQ-9: Patient Health Questionnaire
PPD: postpartum depression
SNRI: serotonin-norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant
DSM: Diagnostic and Statistical Manual of Mental Disorders

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
SSRI		
citalopram (Celexa®)	20 mg PO once daily; may increase to 40 mg PO once daily after one week	40 mg/day (≤ 60 years) 20 mg/day (> 60 years)
escitalopram (Lexapro®)	10 mg PO once daily; may increase to 20 mg PO once daily after 1 week	20 mg/day
fluoxetine (Prozac®)	Prozac: 20 mg PO once daily; may increase by 10-20 mg after several weeks Prozac Weekly: 90 mg PO q week beginning 7 days after the last daily dose	Prozac: 80 mg/day Prozac Weekly: 90 mg/week
paroxetine (Paxil®, Paxil CR®, Pexeva®)	Paxil, Pexeva: 20 mg PO once daily; may increase by 10 mg every week as needed Paxil CR: 25 mg PO once daily; may increase by 12.5 mg every week as needed	Paxil, Pexeva: 50 mg/day Paxil CR: 62.5 mg/day
sertraline (Zoloft®)	50 mg PO once daily; may increase every week as needed	200 mg/day
SNRIs		
duloxetine (Cymbalta®)	20 mg or 30 mg PO twice daily or 60 mg PO once daily	120 mg/day
venlafaxine (Effexor XR®)	Effexor: 75 mg/day PO in 2-3 divided doses; may increase by 75 mg every 4 days as needed Effexor XR: 75 mg PO once daily; may increase by 75 mg every 4 days as needed	Effexor: 225 mg/day (outpatient) or 375 mg/day (inpatient) Effexor XR: 225 mg/day
desvenlafaxine (Pristiq®)	50 mg PO once daily	400 mg/day
Fetzima® (levomilnacipran)	20 mg PO once daily for 2 days, then 40 mg PO once daily; may increase by 40 mg every 2 days	120 mg/day
TCAs		
amoxapine	25 to 300 mg/day PO in divided doses	400 mg/day (300 mg/day if geriatric)
clomipramine* (Anafranil®)	12.5 to 150 mg/day PO once daily	250 mg/day (200 mg/day if pediatric)
desipramine (Norpramin®)	25 to 300 mg/day PO once daily	300 mg/day (100 mg/day if pediatric)
nortriptyline (Pamelor®)	25 to 150 mg/day PO once daily	150 mg/day
Other Antidepressants		
bupropion (Aplenzin®, Forfivo XL®, Wellbutrin SR®, Wellbutrin XL®)	Varies	Immediate-release: 450 mg/day (300 mg/day if pediatric) Sustained-release: 400 mg/day

Drug Name	Dosing Regimen	Maximum Dose
		Extended-release (HCl): 450 mg/day Extended-release (HBr): 522 mg/day
mirtazapine (Remeron®)	15 to 45 mg PO once daily	45 mg/day

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None.
- Boxed Warning(s):
  - Excessive sedation and sudden loss of consciousness during administration. Patients must be monitored for excessive sedation and sudden loss of consciousness and have continuous pulse oximetry monitoring. Because of these risks, Zulresso® is available only through a restricted program under a REMS program.

APPENDIX D: General Information

- HAM-D scale is a 17-item depression assessment scale to assess severity of, and change in, depressive symptoms.

HAM-D Score	Depression Rating
0 – 7	Normal
≥ 20	At least moderate severity

- MADRS is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders.

MADRS Score	Depression Rating
0 – 6	Normal/symptom absent
7 – 19	Mild depression
20 – 34	Moderate depression
> 34	Severe depression

- PHQ-9 is a 9-item multiple choice questionnaire used for diagnosis, screening, monitoring and measuring the severity of depression.

PHQ-9 Score	Depression Severity
5 – 9	Mild depression
10 – 14	Moderate depression
15 – 19	Moderately severe depression
> 20	Severe depression

References

1. Zulresso® Prescribing Information. Cambridge, MA: Sage Therapeutics, Inc.; June 2019. Available at: www.zulresso.com. Accessed October 8, 2020.

2. Meltzer-Brody S, Colquhoun H, Riesenberg R, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet. 2018 Sep 22;392(10152):1058-1070. Accessed October 8, 2020.
3. American College of Obstetricians and Gynecologists. Postpartum depression (December 2013). Available at: https://www.acog.org/Patients/FAQs/Postpartum-Depression. Accessed October 8, 2020.
4. National Institute for Health and Care Excellence. Antenatal and postnatal mental health: clinical management and service guidance. Clinical guideline [CG192]. Available at: https://www.nice.org.uk/guidance/cg192. Accessed October 8, 2020.
5. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder, third edition. November 2010. Available at: http://psychiatryonline.org/guidelines.aspx. Accessed October 8, 2020.
6. Hamilton Depression Rating Scale (HDRS). Available at: https://dcf.psychiatry.ufl.edu/files/2011/05/HAMILTON-DEPRESSION.pdf. Accessed October 8, 2020.
7. Montgomery–Åsberg Depression Rating Scale. Available at: http://www.liquisearch.com/montgomery%E2%80%93%C3%85sberg_depression_rating_sc ale/interpretation. Accessed October 8, 2020.
8. Patient Health Questionnaire (PHQ-9). Available at: https://www.statisticssolutions.com/patient-health-questionnaire-phq-9/. Accessed October 8, 2020.
9. Sharp, Rachel. The Hamilton rating scale for depression. Occupational Medicine. 2015; 65(4):340. Accessed October 8, 2020.
10. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–613. Accessed October 8, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Line of business policy applies was updated to “all lines of business”. 2. Initial approval criteria was updated to include definition of postpartum depression. 3. Appendix A was updated to include additional abbreviations. 4. Appendix B language was rephrased to “below are suggested therapeutic alternatives based on clinical guidance…”. Also updated to remove discontinued drugs. 5. Appendix C was updated for accuracy (boxed warning and contraindications were switched). 6. References were updated.	10/08/2020	12/07/2020