Pharmacy Management Drug Policy

SUBJECT: Gamma-Aminobutyric Acid (GABA) A Receptor Positive Modulators for Postpartum Depression
POLICY NUMBER: PHARMACY- 82
EFFECTIVE DATE: 6/20/2019
LAST REVIEW DATE: 03/06/2025

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Zulresso™ (brexanolone), is a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator, that was the first FDA-approved treatment specifically for postpartum depression (PPD). It is indicated in patients 15 years of age and older and is administered as a continuous intravenous (IV) infusion given over 60 hours. Zurzuvae™ (zuranolone) is also a neuroactive steroid gamma-aminobutyric acid (GABA) A receptor positive modulator that is indicated for the treatment of postpartum depression in adults. It is the first FDA approved oral treatment for postpartum depression and is taken once daily for 14 days.

The active ingredient of Zulresso™, brexanolone, is chemically identical to allopregnanolone, an endogenous metabolite of progesterone. During pregnancy, plasma concentrations of allopregnanolone increase, then subsequently decrease substantially after childbirth. These changes are thought to contribute to PDD as fluctuations in allopregnanolone levels have demonstrated effects on anxiety and depression in animal studies. The mechanism of action of the active ingredient of Zurzuvae™, zuranolone, in the treatment of postpartum depression is not fully understood but is thought to be related to its positive allosteric modulation of gamma-aminobutyric acid (GABA) A receptors.

According to the American College of Obstetricians and Gynecologists (ACOG), perinatal depression (occurring during pregnancy or within the first postpartum year) affects approximately one in seven women (14%); with onset occurring before pregnancy in 27% of patients, during pregnancy in 33% of patients, and postpartum in 40% of patients. As with other forms of depression, PPD 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.

ACOG Clinical Practice Guidelines for the Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum (2023) recommend that screening for perinatal depression occur at the initial prenatal visit, later in pregnancy near or in the third trimester, and at postpartum visits. ACOG notes that there are numerous acceptable screening instruments designed to detect perinatal

depression, with the most commonly used standardized, validated tools being the Edinburgh Postnatal Depression Scale (EDPS) or the Patient Health Questionnaire-9 (PHQ-9).

The U.S. Preventative Services Task Force (USPSTF) recommends depression screening in the general adult population, including pregnant and postpartum women (B recommendation, 2019). Clinicians should provide or refer pregnant women and women less than 1 year postpartum who are at increased risk of perinatal depression to counseling recommendations.

The American Academy of Pediatrics (AAP) recommends that pediatricians integrate surveillance and screening at the 1-, 2-, 4-, and 6-month visits using the Edinburgh scale as unrecognized maternal depression can cause failure-to-thrive and other pediatric issues (2019).

POLICY:

I. Zulresso (brexanolone injection) - Medical Benefit

1. Zulresso must be prescribed by a psychiatrist, psychiatric nurse practitioner or an obstetrician-gynecologist in consultation with a psychiatrist or psychiatric nurse practitioner, **AND**
2. The patient must be at least 15 years of age, **AND**
3. The patient must have a diagnosis, confirmed by a psychiatrist, psychiatric nurse practitioner or an obstetrician-gynecologist in consultation with a psychiatrist or psychiatric nurse practitioner, of **severe** Postpartum Depression (PPD), based on an ACOG supported validated tool (See Supplemental Information), with documentation of a major depressive episode that occurred between the 3rd trimester through 4 weeks postpartum. There must also be documentation of serious functional decline or an inability to function with potential for harm to themselves or others.
   a. The major depressive episode must meet the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for a major depressive episode as outlined in table 1 (See Supplemental Information), **AND**
4. Documentation must be submitted which confirms the treatment facility and patient are registered through the Zulresso REMS program, **AND**
5. The patient must be no more than 6 months postpartum and not currently pregnant, **AND**
6. **Step Therapy Applies:** Patient must have serious side effects or drug failure with Zurzuvae. This applies to all lines of business except Medicare Part B.
7. Approval will be for 1 month to allow for a one-time administration of Zulresso over 60 hours
   a. FDA approved dosing for Zulresso (as a continuous IV infusion):
   b. 0 to 4 hours: 30 mcg/kg/hour
   c. 4 to 24 hours: 60 mcg/kg/hour
   d. 24 to 52 hours: 90 mcg/kg/hour **OR** 60 mcg/kg/hour for those who do not tolerate 90mcg/kg/hour
   e. 52 to 56 hours: 60 mcg/kg/hour
   f. 56 to 60 hours: 30 mcg/kg/hour

II. Zurzuvae (zuranolone capsules) – Pharmacy Benefit

1. Zurzuvae must be prescribed by a psychiatrist, psychiatric nurse practitioner or an obstetrician-gynecologist in consultation with a psychiatrist or psychiatric nurse practitioner, **AND**

2. Patient must be 18 years of age or older, **AND**

3. Patient must have diagnosis, confirmed by a psychiatrist, psychiatric nurse practitioner, or an obstetrician-gynecologist in consultation with a psychiatrist or psychiatric nurse practitioner, of severe Postpartum Depression (PPD), based on an ACOG supported validated tool, with documentation of a major depressive episode that occurred between the 3rd trimester though 4 weeks postpartum, **AND**

4. The patient must be no more than 6 months postpartum and not currently pregnant, **AND**

5. **Step Therapy Applies:** Patient must have had serious side effects or a drug failure of a generic SSRI or SNRI, **AND**

6. Maximum of 1 treatment course (14 days) allowed per a single postpartum period (up to 12 months following delivery)

7. Approval will be for 1 month to allow for one 14-day treatment course

8. Quantity limit:
   a. 20 mg: 28 capsules/14 days
   b. 25 mg: 28 capsules/14 days
   c. 30 mg: 14 capsules/14 days

SUPPLEMENTAL INFORMATION:

Table 1. Diagnostic Criteria for a Major Depressive Episode

		Criteria
A	Five or more symptoms for 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
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	

Adapted from FDA Briefing Document[10] and Diagnostic and Statistical Manual of Mental Disorders: DSM-5. 5th ed., American Psychiatry Association, 2013.[7]

Validated tools supported by the American College of Obstetricians and Gynecologists (ACOG) committee:

- Edinburgh Postnatal Depression Scale
- Postpartum Depression Screening Scale
- PHQ-9 depression questionnaire
- Beck Depression Inventory
- Beck Depression Inventory-II
- Center for Epidemiologic Studies Depression Scale
- Zung Self-Rating Depression Scale

POLICY GUIDELINES:

1. Non-FDA approved indications for Zulresso will not be approved.
2. Dose and frequency should be in accordance with the FDA label or recognized compendia (for off-label uses). When services are performed in excess of established parameters, they may be subject to review for medical necessity.
3. This policy is subject to frequent revisions as new medications come onto the market. Some drugs will require prior authorization prior to approved language being added to the policy.
4. Prior authorization is contract dependent.
5. This policy is applicable to drugs that are included on a specific drug formulary. If a drug referenced in this policy is non-formulary, please reference the Coverage Exception Evaluation Policy for All Lines of Business Formularies policy for review guidelines.
6. This policy does not apply to Medicare Part D and D-SNP pharmacy benefits. The drugs in this policy may apply to all other lines of business including Medicare Advantage.
7. For members with Medicare Advantage, medications with a National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) will be covered pursuant to the criteria outlined by the NCD and/or LCD. NCDs/LCDs for applicable medications can be found on the CMS website at https://www.cms.gov/medicare-coverage-database/search.aspx. Indications that have not been addressed by the applicable medication's LCD/NCD will be covered in accordance with criteria determined by the Health Plan (which may include review per the Health Plan's Off-Label Use of FDA Approved Drugs policy). Step therapy requirements may be imposed in addition to LCD/NCD requirements.
8. Clinical documentation must be submitted for each request (initial and recertification) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments/treatment history, diagnostic testing, laboratory test results, genetic testing/biomarker results, imaging and other objective or subjective measures of benefit which support continued use of the product.
9. All requests will be reviewed to ensure they are being used for an appropriate indication and may be subject to an off-label review in accordance with our Off-Label Use of FDA Approved Drugs Policy (Pharmacy-32).
10. All utilization management requirements outlined in this policy are compliant with applicable New York State insurance laws and regulations. Policies will be reviewed and updated as necessary to ensure ongoing compliance with all state and federally mandated coverage requirements.

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. Codes may not be covered under all circumstances. Please read the policy and guideline statements carefully. Codes may not all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.

Code Key: Experimental/Investigational = (E/I). Not medically necessary/appropriate = (NMN).

HCPCS:

Description (Number): **Zulresso (J1632)**

UPDATES:

Date	Revision
03/06/2025	Revised
12/19/2024	Revised

09/13/2024	Revised
08/15/2024	Reviewed / P&T Committee Approval
06/20/2024	Revised
04/01/2024	Revised
08/24/2023	P&T Committee Approval
07/18/2023	Reviewed
03/14/2023	Revised
08/09/2022	Revised
07/2022	P&T Committee Approval
05/2022	Reviewed
7/2021	Reviewed & P&T Committee Approved
06/2021	Reviewed
09/2020	Reviewed & P&T Committee Approved
01/2020	Revised
10/2019	Revised
09/2019	P&T Approval
06/2019	Created

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