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Policy Number: C27296-A

Zurzuvae (zuranolone)

PRODUCTS AFFECTED

Zurzuvae (zuranolone)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Postpartum Depression (PPD)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by-case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. POSTPARTUM DEPRESSION:

1. Documented diagnosis of moderate to severe Postpartum Depression (PPD)
   AND
2. Documentation of onset of symptoms in the third trimester or within 4 weeks of delivery [DOCUMENTATION REQUIRED]
   AND
3. Prescriber attestation that the member's baseline moderate to severe postpartum depression (PPD) symptoms are measured and documented by a rating scale (such as the Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Åsberg Depression Rating Scale (MADRS) with a score of ≥ 20), or Edinburgh Postnatal Depression Scale (EPDS) OR as documented by a comparable standardized rating scale that reliably measures depressive symptoms (See Appendix)
   AND
4. Member is 12 months or less postpartum at initiation of Zurzuvae (zuranolone) therapy
   AND
5. Prescriber attests other diagnoses such as postpartum blues, postpartum psychosis, bipolar disorder, hypo- or hyperthyroidism, and postpartum anemia have been ruled out
   AND
6. Member has ceased lactating OR prescriber attests if still lactating or actively breastfeeding, member has been counseled on risk
   AND
7. Prescriber attests that member has had a negative pregnancy screening and has been counseled on the use of effective contraception during treatment and per FDA labeled recommendations
   AND
8. (a) Documentation of inadequate response (8 week trial), serious side effects, or contraindication to ONE of the following at a maximally tolerated therapeutic dose:
   i. Selective serotonin reuptake inhibitor (SSRI) (e.g., paroxetine, sertraline, citalopram)
   ii. Serotonin- norepinephrine reuptake inhibitor (SNRI) (e.g., desvenlafaxine, duloxetine, venlafaxine)
   iii. Tricyclic antidepressant (TCA) (e.g., nortriptyline)
   iv. Bupropion
   v. Mirtazapine

   OR

   (b) Documentation of clinical rationale supporting an exception of an oral antidepressant trial as determined by Prescriber (i.e., member is a potential risk of harm to self and/or others as determined by the treating provider)
   MOLINA REVIEWER NOTE: For Nevada Marketplace, please see Appendix.
   AND
9. For members who have received Zurzuvae therapy for a previous pregnancy/post-partum period: Prior therapy with Zurzuvae (zuranolone) resulted in improvement of depressive symptoms AND did not experience serious adverse effects, including: excessive somnolence or confusion, worsening depression or emergent suicidal thoughts and behaviors

CONTINUATION OF THERAPY:
NA; Authorizations are granted for one treatment per postpartum period per delivery.

DURATION OF APPROVAL:
Initial authorization: 3 months (14 days of treatment total), Continuation of Therapy: NA

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a board-certified Psychiatrist or OB/GYN [If prescribed in consultation, consultation notes must be submitted with initial request]

AGE RESTRICTIONS:
18 years of age and older

QUANTITY:
50 mg orally once daily in the evening for 14 days

Maximum Quantity Limits – 14 days per treatment authorization
The safety and effectiveness of Zurzuvae use beyond 14 days in a single treatment course have not been established.

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
GABA Receptor Modulator – Neuroactive Steroid

FDA-APPROVED USES:
Indicated for the treatment of postpartum depression (PPD) in adults

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:

Reserved for State specific information. *Information includes, but is not limited to, State contract language, Medicaid criteria and other mandated criteria.*

State Specific Information
State Marketplace
Nevada (Source: Nevada Legislature)
"Chapter 689A of Nevada Revised Statutes (NRS) is hereby amended by adding thereto a new section to read as follows:

1. A policy of health insurance which provides coverage for prescription drugs must not require an insured to submit to a step therapy protocol before covering a drug approved by the Food and Drug Administration that is prescribed to treat a psychiatric condition of the insured, if:
    a. The drug has been approved by the Food and Drug Administration with indications for the psychiatric condition of the insured or the use of the drug to

treat that psychiatric condition is otherwise supported by medical or scientific evidence;

b. The drug is prescribed by:
    i. A psychiatrist
    ii. A physician assistant under the supervision of a psychiatrist;
    iii. An advanced practice registered nurse who has the psychiatric training and experience prescribed by the State Board of Nursing pursuant to NRS 632.120; or
    iv. A primary care provider that is providing care to an insured in consultation with a practitioner listed in subparagraph (1), (2) or (3), if the closest practitioner listed in subparagraph (1), (2) or (3) who participates in the network plan of the insurer is located 60 miles or more from the residence of the insured; and
c. The practitioner listed in paragraph (b) who prescribed the drug knows, based on the medical history of the insured, or reasonably expects each alternative drug that is required to be used earlier in the step therapy protocol to be ineffective at treating the psychiatric condition…

3. As used in this section:
    c. *'Step therapy protocol' means a procedure that requires an insured to use a prescription drug or sequence of prescription drugs other than a drug that a practitioner recommends for treatment of a psychiatric condition of the insured before his or her policy of health insurance provides coverage for the recommended drug*."

Molina Reviewer Note: Medical necessity review for a psychiatric condition cannot require trial of other medications first. This is applicable to formulary medications that require prior authorization and non-formulary medications and is not limited to only medications designated 'ST'. If the requested drug is a brand name and the generic is on formulary, request can be reviewed for specific medical reason generic cannot be used.

Appendix 1: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5): Diagnostic criteria for a major depressive episode

A. Five (or more) of the following symptoms have been present during the same two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
NOTE: Do not include symptoms that are clearly attributable to another medical condition.
1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observations made by others (e.g., appears tearful). (NOTE: In children and adolescents, can be irritable mood.)
2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. (NOTE: In children, consider failure to make expected weight gain.)
4) Insomnia or hypersomnia nearly every day
5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6) Fatigue or loss of energy nearly every day
7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self- reproach or guilt about being sick)

8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by their subjective account or as observed by others)
9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the direct physiological effects of a substance or to another medical condition.
NOTE: Criteria A through C represent a major depressive episode.
NOTE: Responses to a significant loss (e.g., bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgement based on the individual's history and the cultural norms for the expression of distress in the context of loss.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic or hypomanic episode.
NOTE: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.
Specify:
With anxious distress
With mixed features
With melancholic features
With atypical features
With psychotic features
With catatonia
With peripartum onset
With Seasonal pattern

Reference: Langan, R. Identification and Management of Peripartum Depression. Am Fam Physician. 2016 May 15;93(10):852-858. https://www.aafp.org/afp/2016/0515/p852.html --Reprinted with permission from the American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, DC: American Psychiatric Association; 2013:160–161.

Appendix 2:
Common Screening Tests for Peripartum Depression

American Academy of Family Physicians (AAFP) recommend screening at the postpartum visit, or 2-month well- child visit (Am Fam Physician 2010 Oct 15;82(8):926)

American College of Obstetricians and Gynecologists (ACOG) Committee Opinion 757 on

screening for perinatal depression

- Screen women at least once during perinatal period for depression and anxiety using a validated, standardized screening tool
- Close monitoring, evaluation, and assessment is recommended in women with current depression or anxiety, history of perinatal mood disorders, risk factors for mood disorders

Edinburgh Postnatal Depression Scale (EPDS) was published over 30 years ago and is a self-reported scale used internationally to assess depression during pregnancy and postpartum

- EPDS is most frequently used tool in research and clinical settings; available in 50 different languages and can be completed in < 5 minutes. Criteria supported by ACOG Committee Opinion 757 on screening for perinatal depression (ACOG 2018 Oct)
- 10-item questionnaire, with each question scored from 0 to 3, and a maximum score of 30
- can be used as early as 3 days postpartum with a score > 9.5 indicating possible depression
- likely major or minor depression indicated by score > 12 in pregnancy, or > 10 in postpartum period
- Calculator available at: https://psychology-tools.com/test/epds

Reference: Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. Br J Psychiatry. 1987 Jun;150:782-6. PMID:3651732

Hamilton Rating Scale for Depression (HAM-D) is a validated 17-item rating scale used to determine the severity level of depression in a patient before, during, and after treatment. This scale is an accepted regulatory endpoint for depression. The scale is used to rate the severity of a patient's depression by probing mood, feelings of guilt, suicide ideation, insomnia, agitation, anxiety, weight loss, and somatic symptoms. 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

https://qxmd.com/calculate/calculator_146/hamilton-depression-rating-scale-ham-d-or-hdrs

Montgomery-Asberg Depression Rating Scale (MADRS) is a 10-item diagnostic questionnaire used to measure the severity of depressive episodes in patients with mood disorders.

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

https://www.mdcalc.com/montgomery-asberg-depression-rating-scale-madrs

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

PHQ-9	Depression Severity
5 – 9	Minimal symptoms
10 – 14	Minor depression Major depression, mild
15 – 19	Major depression, moderately severe
> 20	Major depression, severe

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Postpartum depression (PPD), also known as major depressive disorder with peripartum onset, is defined by the onset of depressive symptoms, unipolar major depressive disorder, or mood disorder in the postpartum period (onset 4-6 weeks following delivery for up to 1 year). The Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) classifies peripartum depression as a major depressive disorder that is identified during pregnancy or within four weeks postpartum, although some experts extend this to within one year postpartum. The DSM-5 does not recognize PPD as a separate diagnosis; rather, PPD patients meet the criteria for a major depressive episode and the criteria for peripartum onset. The DSM-5 criteria for major depressive disorder are listed in **Appendix 1.** It is estimated that PPD affects approximately 10-20 %of women giving birth globally. In the United States, estimates of new mothers identified with PDD each year vary by state from 8-20 %, with an overall average of 11.5 % (Sage Therapeutics). The Centers for Disease Control and Prevention estimates that 1 in 9 women, and possibly as many as 1 in 5, experience PPD. The etiology of PPD is unknown, but a rapid decline in reproductive hormone levels after delivery is thought to trigger mood disorder in susceptible women. Risk factors include personal or family history of antenatal or postpartum depression. Preventive therapy is recommended for at-risk women, including prenatal and postpartum counseling, psychotherapy, and/or previously used antidepressant medication. Primary care clinicians (including obstetricians, gynecologists, or pediatricians) should screen all postpartum women for depression at least once during the perinatal period (at the postpartum visit or 2-month well-child visit) with the Edinburgh Postnatal Depression Scale (EDPS) or other screening tool. Treatment of PPD depends on the severity of symptoms and the level of functional impairment. 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 (National Institute of Mental Health). Psychotherapy alone is considered first-line treatment for mild to moderate peripartum depression, whereas psychotherapy is often combined with medication in patients with severe symptoms. Cognitive behavior therapy has the most evidence supporting its effectiveness. Pharmacological treatment options included: SSRIs, Serotonin and norepinephrine reuptake inhibitors (SNRIs), Monoamine oxidase inhibitors (MAOIs), or Tricyclic antidepressants (TCAs). (Molyneaux E, et al.) SSRIs are the most commonly prescribed antidepressant (Langan et al., 2016). However, SSRI agents are not specifically FDA-approved for the treatment of PPD and can often take weeks to months to be effective in alleviating symptoms of depression. No substantial evidence supports the use of one SSRI over another, although there are a few factors to consider when selecting an agent for postpartum women including sensitivity to medications due to hormone effects on liver enzymes, increased volume of distribution, and increased levels of drug-binding proteins; therefore, some experts recommend starting a medication at one-half of the regular dose and titrating slowly. Generally, Celexa (citalopram), Lexapro (escitalopram), or Zoloft (sertraline) is recommended first- line during pregnancy or while breastfeeding, due to minimal risks to the fetus/neonate. However, when these agents cannot be used or are ineffective, alternatives include bupropion, Pristiq (desvenlafaxine succinate ER), Cymbalta (duloxetine DR), Prozac (fluoxetine), Remeron (mirtazapine), venlafaxine, and TCAs. While the use of pharmacotherapy during breastfeeding is a concern, the risks must be weighed against the risks of untreated PPD to the woman and her children, including suicide risk and impaired maternal- infant bonding.

The safety and efficacy of Zurzuvae (zuranolone) was evaluated in two randomized, placebo-

controlled, double-blind, multicenter studies (Study 1, SKYLARK, NCT04442503 and Study 2, ROBIN, NCT02978326) in women with PPD who met the Diagnostic and Statistical Manual of Mental Disorders criteria for a major depressive episode (DSM-5 for Study 1, and DSM-IV for Study 2) with onset of symptoms in the third trimester or within 4 weeks of delivery. Concomitant us of existing oral antidepressants was allowed in patients taking a stable dose at least 3 days before baseline. Less than 20% of study entrants were on concomitant oral antidepressant. The studies included patients with a HAMD-17 score of 26 or greater at baseline. The primary endpoint was change in HAMD-17 score at day 15. In both studies, patients in the Zurzuvae groups experienced statistically significantly greater improvement on the primary endpoint compared to patients in the placebo groups. Study 1 placebu subtracted difference (95% CI) was -4.0 (-6.3, -1.7) and in study 2 it was -4.2 (-6.9, -1.5). The follow-up period was from Day 15 to Day 45 in both trials. Based on an analysis of the STAR*D trial, a clinically meaningful difference is seen with a 4 to 6 point change in the HAMD-17 scale (Neuropsychiatr Dis Treat, 2021).

Zurzuvae was generally well tolerated and had a consistent safety profile across both PPD studies. The most common side effects with an incidence >5% and greater than placebo in patients treated with Zurzuvae 50 mg were somnolence, dizziness, diarrhea, fatigue, and urinary tract infection.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Zurzuvae (zuranolone) are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Zurzuvae (zuranolone) include: no labeled contraindications. Avoid concomitant use of Zurzuvae with CYP3A4 inducers.

OTHER SPECIAL CONSIDERATIONS:
Zurzuvae contains zuranolone, a Schedule IV controlled substance under the Controlled Substances Act.

Zurzuvae (zuranolone) has a Black Box Warning for impaired ability to drive or engage in other potentially hazardous activities. Zurzuvae causes driving impairment due to central nervous system (CNS) depressant effects. Advise patients not to drive or engage in other potentially hazardous activities until at least 12 hours after administration. Patients may not be able to assess their own driving competence or the degree of impairment caused by Zurzuvae. The prescribing information warns that people who take Zurzuvae should not drive a motor vehicle or engage in other potentially hazardous activities that require complete mental alertness until at least 12 hours after Zurzuvae administration for the duration of the 14-day treatment course.

The inclusion criteria for both SKYLARK and ROBIN required patients to have ceased lactating or, if still lactating or actively breastfeeding at screening, patient had to agree to temporarily cease giving breastmilk to her infant(s). The FDA label does not limit use in lactation.

CODING/BILLING INFORMATION

CODING DISCLAIMER. *Codes listed in this policy are for reference purposes only and may not be all-inclusive or applicable for every state or line of business. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and*

facilities are expected to utilize industry-standard coding practices for all submissions. Molina has the right to reject/deny the claim and recover claim payment(s) if it is determined it is not billed appropriately or not a covered benefit. Molina reserves the right to revise this policy as needed.

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Zurzuvae CAPS 20MG
Zurzuvae CAPS 25MG
Zurzuvae CAPS 30MG

REFERENCES

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Quantity Background Other Special Considerations	Q1 2026
REVISION- Notable revisions: Required Medical Information References	Q1 2025
NEW CRITERIA CREATION	Q1 2024