

Prior Authorization Update: Fezolinetant

Plain Language Summary:

- Fezolinetant, approved by the Food and Drug Administration in 2023, is used to relieve hot flashes due to menopause. Fezolinetant is not a hormone, like estrogen or progestin. This update will look at recent evidence to ensure the fezolinetant prior authorization (PA) criteria are up to date.
- Menopause typically occurs between the age of 45 to 55 years in women. Menopause can result in hot flashes and night sweats which are also called vasomotor symptoms. Sometimes these symptoms can be severe enough to interrupt sleep or cause anxiety and depression.
- The hormones estrogen and progestin are very effective in reducing how often hot flashes happen and how severe hot flashes feel in women going through menopause. However, estrogen use can increase risk of cancer, stroke, and blood clots. Estrogens that are put on the skin have a lower risk of breast cancer than estrogens taken by mouth, but the risk is still increased compared to taking no estrogen. People that have a uterus should take estrogen *with* a progestin to reduce the risk of uterine cancer.
- In two clinical trials that compared fezolinetant with placebo over 12 weeks, the severity and frequency of hot flashes was reduced by half in postmenopausal women who received fezolinetant 45 mg tablets.
- Side effects reported with fezolinetant included stomach pain, diarrhea, back pain, and increases in tests that look at liver function. The manufacturer recommends getting liver function tests before starting fezolinetant and checking liver function periodically during the first year of treatment.
- Estrogen medicines are paid for by fee-for-service Medicaid. Fezolinetant and certain estrogen medicines require the provider to explain why the specific estrogen is needed before paying for it. This is called a prior authorization.

Purpose of Update: Review additional evidence for the safety and efficacy of fezolinetant to ensure prior authorization criteria are up to date.

Background:

Menopause typically occurs between the age of 45 to 55 years, with a mean age of onset around 51 years. Approximately 60% to 80% of women experience vasomotor symptoms, 20% of them are considered severe symptoms.¹ Hot flashes and night sweats are considered primary vasomotor symptoms that may also be associated with sleep and mood disturbances, as well as decreased cognitive function.² These symptoms occur as episodes that usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety, and on occasion, heart palpitations.³ Vasomotor symptoms can persist on average of 7 to 10 years.⁴ Prevalence of vasomotor symptoms varies between different ethnic groups and cultures, with a higher incidence and longer duration of symptoms in Black and Hispanic women.¹ In all racial/ethnic groups, vasomotor symptoms increase as women progress from pre-menopause to early perimenopause and even more dramatically as they make the transition to late perimenopause.¹ Other risk factors related to severity of vasomotor symptoms include older age, body mass index greater than 30 kg/m², lower education level (college-educated versus less than a college education), smoking history longer than 40 pack-years, and high baseline anxiety or depression scores.¹

The neurokinin 3 receptor antagonist, fezolinetant, received FDA-approval May 2023 for the management of moderate-to-severe vasomotor symptoms associated with menopause.⁵ Two phase 3 clinical trials, Skylight 1 and Skylight 2, contribute to the safety and efficacy data for this indication.^{6,7} In these

identically designed trials, a total of 1022 of postmenopausal patients identified as women at birth, aged 45 years to 60 years who had a minimum average of 7 moderate to severe vasomotor symptoms per day were randomized to oral fezolinetant 30 mg, 45 mg, or placebo once day over 12 weeks.^{6,7} After completing 12 weeks of treatment, patients receiving placebo were re-randomized to fezolinetant 30 mg or 45 mg daily for an additional 40 weeks.^{6,7}

The 2 co-primary endpoints studied in both trials were mean change in frequency (a reduction of at least 2 events per day was considered clinically significant) and change in severity of moderate-to-severe vasomotor symptoms at Weeks 4 and 12.^{6,7} Severity of vasomotor symptoms was defined as mild, moderate, or severe and recorded in a daily electronic diary by study participants.^{6,7} The severity score of mild, moderate, and severe vasomotor symptoms was coded as 1, 2, and 3, respectively, with higher scores indicating greater severity.^{6,7} Only the fezolinetant 45 mg dosing group met the clinical threshold of superiority in symptom frequency compared with placebo at Weeks 4 and 12.⁴ In Skylight 1 and Skylight 2, the least squares mean (LSM) differences in the change from baseline of vasomotor symptoms per day were lower in fezolinetant 45 mg recipients than placebo recipients at Week 4 (–2.07 and –2.55, respectively; $p < 0.01$; moderate-quality evidence).^{6,7} Similar results were observed with fezolinetant 45 mg versus placebo in reduction of symptom severity on the 3-point scale at week 4 (LSM difference: –0.19 and –0.29; $p < 0.01$; moderate-quality evidence).^{6,7} In both trials, decreases in frequency at Week 12 (LSM difference: –2.53 and –2.55 vasomotor events/day; $p < 0.01$) and severity (LSM difference: –0.20 and –0.29; $p < 0.01$; moderate-quality evidence for both endpoints) were also reported with placebo versus fezolinetant 45 mg.^{6,7}

The most common adverse effects reported with fezolinetant include abdominal pain, diarrhea, insomnia, back pain and hepatic transaminase elevations.⁵ Hepatic transaminase elevations greater than 3-times the upper limit of normal (ULN) were elevated approximately 2-fold greater in 45 mg fezolinetant-treated patients compared with placebo-treated patients.⁸ These hepatic transaminase elevations occurred at various timepoints in the 12-month clinical trial, were generally transient, and resolved while on fezolinetant 45 mg or shortly after discontinuation.⁸ Based on this observation, the manufacturer recommends assessing hepatic function, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin (total and direct) at baseline, in addition to monitoring these parameters after initiating fezolinetant treatment.⁵ In the 52-week, phase 3 RCT (Skylight 4) there was an imbalance in malignancies in the fezolinetant treatment groups and placebo, however the FDA reviewers concluded that this appeared to be a chance finding without evidence of a causal relationship between fezolinetant and malignancy.⁴

In September 2024 the FDA issued a drug safety report that fezolinetant can cause rare but serious liver injury based on a postmarketing case reported in a patient who developed symptomatic acute mixed hepatocellular cholestatic liver injury with elevated liver function tests within 40 days of starting fezolinetant, which resolved upon discontinuation.⁹ The FDA added new recommendations for patients and health care professionals to increase the frequency of liver blood testing, adding monthly testing for 3 months after starting fezolinetant, and then at months 6 and 9 of treatment as already recommended.⁹ The updated prescribing information also instructs patients to stop the medicine immediately and contact the health care professional who prescribed the medicine if signs and symptoms of liver injury occur.⁹ In December 2024 the FDA added a black boxed warning to fezolinetant labeling.⁵ The warning was added to highlight the known risk of rare but serious liver injury associated with the use of fezolinetant.

Guideline Recommendations:

Systemic menopausal hormone therapy with estrogen alone or, in patients with a uterus, in combination with progestin is first-line treatment for vasomotor symptoms of menopause according to American College of Obstetricians and Gynecologists (ACOG), North American Menopause Society (NAMS), and Endocrine Society.¹⁰ Guidance from the 2022 NAMS position statement considers estrogen containing products (oral, topical or vaginal) the most effective treatment for bothersome vasomotor symptoms and should be considered in women without contraindications who need additional treatment for menopausal symptoms.¹¹ Contraindications to estrogen treatment include women with a history of breast cancer, hepatic disease, cardiovascular disease, stroke, or a venous thromboembolism event (VTE).¹¹ In addition, women over the age of 60 years and/or those who are greater than 10 years from the onset of menopause should

not use hormone therapy due to an unfavorable risk-to-benefit ratio.¹¹ In women with an intact uterus, estrogen is given in combination with progestin to prevent endometrial hyperplasia or carcinoma.¹² Systemic estrogen alone or combined with a progestin reduces the frequency of vasomotor symptoms by approximately 75% compared with placebo.¹³ A reduction in 50% or more in the severity of vasomotor symptoms is considered a clinically meaningful effect.¹² In clinical trials, a reduction of at least 2 moderate to severe hot flashes per day is considered a clinically significant reduction in frequency of symptoms.⁸ FDA guidance for treatment of genitourinary symptoms related to menopause in the absence of indications for systemic estrogen therapy suggests the use of low-dose topical vaginal estrogen.¹¹

Hormone therapy remains the most effective treatment and should be considered in menopausal women aged younger than 60 years, within 10 years of their final menstrual period, and without contraindications.¹⁰ For women who are not good candidates for hormone therapy because of contraindications or personal preference, there are nonhormonal treatment options for reducing vasomotor symptoms. The 2015 National Institute for Health and Care Excellence (NICE) treatment guidelines for vasomotor symptoms recommend hormone therapy as first line treatment, with selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and clonidine as second line options for people who have contraindications to hormone therapy.¹⁴

The 2023 NAMS position statement on nonhormonal therapy for management of menopausal symptoms recommends SSRIs, SNRIs, gabapentin, and oxybutynin.¹⁰ Typically, the onset of action with these medications is within 2 weeks. There are limited trials comparing nonhormone prescription therapies head-to-head with hormone therapy.¹⁰ Evidence exists that SSRIs and SNRIs are associated with mild to moderate improvements in vasomotor symptoms, regardless of whether menopause is natural or surgical, as supported by meta-analyses, a pooled analysis, a Cochrane systematic review, and a review focused on evidence in survivors of cancer.¹⁰ Limitations to these reviews include heterogeneity of the populations and variations in inclusion criteria, as well as variability in the population that was tested, dosing, length of treatment, and outcomes evaluated.¹⁰ Paroxetine, escitalopram, citalopram, venlafaxine, and desvenlafaxine have been shown to reduce vasomotor symptoms in large, double-blind RCTs of symptomatic women.¹⁰ Duloxetine has been found to reduce vasomotor symptoms in smaller studies.¹⁰ Hot flash reductions vary from 25% to 69% with these treatments, with improvements in composite hot flash severity and frequency from 27% to 61%.¹⁰ Trends toward improvement have been seen with sertraline and fluoxetine, but these were not statistically significant; therefore, they are not recommended.¹⁰

A pooled analysis from three RCTs showed that 10 mg to 20 mg of escitalopram, 0.5 mg of estradiol, and 75 mg of venlafaxine daily resulted in comparable reductions in vasomotor frequency.¹⁵ A meta-analysis of 7 RCTs studying the dose of gabapentin 900 mg (300 mg three times/day) shows gabapentin improves the frequency and severity of vasomotor symptoms.¹⁶ Possible adverse events with gabapentin include dizziness, unsteadiness, and drowsiness, typically seen during the first week, with improvement during the second week and resolution by week 4. In a placebo-controlled trial, higher doses of gabapentin (titrated to 2,400 mg/d) were as beneficial as estrogen 0.625 mg/day in reducing hot flash severity scores.¹⁷ Adverse events of gabapentin at this dose included dizziness, headache, and disorientation, which limited its potential benefits.¹⁰ Because drowsiness is an adverse effect, and the half-life is short, bedtime dosing of gabapentin may be a good choice for women with disruptive sleep from vasomotor symptoms.¹⁰ One prospective study and two randomized, double-blind studies in postmenopausal women demonstrated that oxybutynin at doses ranging from 2.5 mg or 5 mg twice daily up to 15 mg extended-release daily significantly improved moderate to severe vasomotor symptoms compared to placebo.¹⁰ Adverse events of oxybutynin are usually dose-dependent and most commonly include a dry mouth and urinary difficulties. Long-term use of anticholinergics may be associated with cognitive decline, particularly in older persons.¹⁰ In summary, nonhormonal pharmacologic therapies to alleviate vasomotor symptoms associated with menopause include SSRIs, SNRIs, gabapentin (high-quality evidence) and oxybutynin (moderate-quality evidence).¹⁰ Fezolinetant is also included in the NAMS position statement as an alternative to hormonal therapy for management of vasomotor symptoms (high-quality evidence).¹⁰

Pharmacologic therapies that are not recommended by NAMS include suvorexant (moderate-quality evidence), clonidine (low to moderate-quality evidence), and pregabalin (low-quality evidence).¹⁰ Suvorexant is a dual orexin-receptor antagonist that blocks the effects of the hypothalamic neuropeptide orexin-A, which promotes wakefulness and may be involved in the occurrences of hot flashes.¹⁰ Postmenopausal women have plasma levels of orexin-A that are three times higher than premenopausal women, which may contribute to sleep disruption and impaired thermoregulation.¹⁰ Suvorexant has been shown to reduce insomnia severity, and findings in a small study of menopausal women showed that it led to reductions in nighttime vasomotor symptoms frequency compared with placebo and was well tolerated.¹⁰ Suvorexant did not improve daytime vasomotor symptoms. Given limited data to support its use, suvorexant is not recommended by NAMS.¹⁰ Clonidine been shown to be modestly more beneficial than placebo but less beneficial than SSRIs, SNRIs, and gabapentin in reducing vasomotor symptoms.¹⁰ It is used infrequently because of adverse effects, including hypotension, lightheadedness, headache, dry mouth, dizziness, sedation, and constipation. Sudden cessation can lead to significant elevations in blood pressure. Because there are other more effective therapies with fewer adverse effects, clonidine is not recommended by NAMS.¹⁰ One phase 3 RCT in 163 women (40% with a history of cancer) evaluated pregabalin for vasomotor symptoms.¹⁸ After 6 weeks of treatment, pregabalin at a dose of 75 mg twice a day or 150 mg twice a day decreased vasomotor symptom frequency by 59% and 61%, respectively, whereas placebo decreased symptoms by 35%.¹⁸ There were more dizziness and cognitive difficulties reported in those taking pregabalin. Because of limited studies, adverse effects including weight gain, and because pregabalin is listed as a Schedule V controlled substance (because of the potential for abuse), pregabalin is not recommended by NAMS.¹⁰

Recommendation:

- Revise PA criteria to stipulate duration of hormonal step therapy, add a recommendation for use of SSRI, SNRI, or gabapentin in addition to hormonal therapy, and add recent FDA guidance for liver function monitoring while taking fezolinetant.

References:

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Appendix 1. Proposed Prior Authorization Criteria

Fezolinetant (Veozah®)

Goal(s):

- To ensure appropriate and safe use of fezolinetant in specified patient populations.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Fezolinetant 45 mg tablets.

Step Therapy Required Prior to Coverage:

- Prevention of vasomotor symptoms: conventional hormone therapy (see preferred drug list options at (www.orpdl.org))
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy previously approved by the FFS program?	Yes: Go to Renewal Criteria	No: Go to #3
3. Is the request to treat moderate to severe vasomotor symptoms due to menopause?	Yes: Go to #4	No: Pass to RPh. Deny; medical appropriateness
4. Does the patient, have inadequate effect, intolerance or contraindication to a 30-day trial of menopausal hormone therapy (e.g., estrogen/progestin)? *Contraindications to estrogen include history of breast cancer, hepatic disease, cardiovascular disease, or a venous thromboembolism event. Intolerance to progestin include breast tenderness and vaginal bleeding.	Yes: Go to #5	No: Pass to RPh. Deny; medical appropriateness Refer provider to preferred drug list option for conventional hormone therapy at www.orpdl.org

Approval Criteria

5. If patient has an intolerance or contraindication to hormonal therapy, do they have an inadequate effect, intolerance or contraindication to a 30-day trial of paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, or gabapentin?	Yes: Go to #6	No: Pass to RPh. Deny; medical appropriateness
6. Is the patient currently taking a CYP1A2 inhibitor (i.e., cimetidine, amiodarone, mexiletine, ciprofloxacin, or fluvoxamine)?	Yes: Pass to RPh. Deny; medical appropriateness. Note: CYP1A2 inhibitors are contraindicated with fezolinetant therapy.	No: Go to #7
7. Have baseline renal function tests been obtained?	Yes: Go to #8 and document baseline labs_____	No: Pass to RPh. Deny; medical appropriateness.
8. Is the estimated glomerular filtration rate (eGFR) < 30 mL/min?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Go to #9
9. Have baseline liver function tests (AST, ALT, Alk Phos, and bilirubin) been obtained?	Yes: Go to #10 and document baseline labs_____	No: Pass to RPh. Deny; medical appropriateness.
10. Do liver function tests (LFTs) indicate presence of severe cirrhosis (i.e., serum transaminase concentrations or total bilirubin greater than 2 times the upper limit of normal)?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Approve for 3 months.

Renewal Criteria		
1. Have frequency and severity of vasomotor symptoms been reduced from baseline with fezolinetant treatment?	Yes: Go to #2	No: Pass to RPh. Deny; medical appropriateness.
2. Have LFTs been requested at months 1-, 2-, and 3 after starting treatment with fezolinetant?	Yes: Go to #3 and document LFT results_____	No: Pass to RPh. Deny; medical appropriateness.
3. Do LFTs indicate severe cirrhosis (i.e., serum transaminase concentrations or total bilirubin greater than 2 times the upper limit of normal)?	Yes: Pass to RPh. Deny; medical appropriateness.	No: Approve for 12 months.

P&T/DUR Review: 2/25 (DM) 6/24 (DM)
 Implementation: 3/10/25; 7/1/24