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New Drug Evaluation: Fezolinetant (Veozah™) tablets

Date of Review: June 2024
Generic Name: fezolinetant

End Date of Literature Search: 03/15/2024
Brand Name (Manufacturer): VEOZAH (Astellas)
Dossier Received: yes

Plain Language Summary:

- Menopause typically occurs between the age of 45 to 55 years in people who identify as women at birth. 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 the very effective in reducing the frequency and severity of hot flashes in women going through menopause. However, use of estrogens can increase risk of cancer, stroke, and blood clots. Estrogens applied to the skin have a lower risk of breast cancer than estrogens taken by mouth, but there is still an increased risk compared to taking no estrogen. People that have a uterus often take estrogen with a progestin to reduce the risk of uterine cancer.
- A new medicine, fezolinetant (VEOZAH), recently approved by the Food and Drug Administration (FDA), is used to treat hot flashes due to menopause. Fezolinetant is not a hormone, like estrogen or progestin. This review will look at the evidence for how well fezolinetant works and side effects caused by this medicine.
- In two clinical trials that compared fezolinetant with placebo, 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.
- Estrogen medicines are paid for by fee-for-service Medicaid. Certain estrogen medicines require the provider to explain why the specific estrogen in needed before paying for it. This is called a prior authorization.
- The Drug Use Research Management Program recommends providers submit prior authorization for fezolinetant in postmenopausal women before fee-for-service Medicaid will pay for it.

Research Questions:

1. What is the efficacy of fezolinetant compared with placebo to reduce moderate-to-severe vasomotor symptoms associated with menopause?
2. What are the harms of fezolinetant compared with placebo when used to reduce vasomotor symptoms associated with menopause?
3. Does fezolinetant differ in effectiveness or harms for any patient subgroups (e.g., smoking status, age, race, or ethnicity)?

Conclusions:

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- The neurokinin 3 receptor antagonist, fezolinetant (VEOZAH), received FDA-approval May 2023 for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.[1] Two phase 3 clinical trials, Skylight 1 and Skylight 2, contribute to the efficacy data for this indication and are evaluated below in **Table 3**.[2,3] 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.[2,3] 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.[2,3]
- 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.[2,3] Severity of vasomotor symptoms was defined as mild, moderate, or severe and recorded in a daily electronic diary by study participants.[2,3] The severity score of mild, moderate, and severe vasomotor symptoms was coded as 1, 2, and 3, respectively, with higher scores indicating greater severity.[2,3] 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). [2,3] 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).[2,3] 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.[2,3]
- Fezolinetant safety was evaluated in Skylight 4, a 52-week, placebo-controlled, phase 3 randomized controlled trial (RCT) conducted in 1,830 postmenopausal women which recorded incidence of treatment emergent adverse events (TEAEs), and the percentage of women with endometrial hyperplasia or endometrial malignancy.[5] The most common adverse effects reported in this RCT included abdominal pain, diarrhea, insomnia, back pain and hepatic transaminase elevations.[1] 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.[6] 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.[6] 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 at 3, 6 and 9 months after initiating fezolinetant treatment.[1] In 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]
- The FDA reviewers completed a subgroup analysis of enrolled participants by smoking status, age, race, and body mass index (BMI).[6] However, the trials were not powered to detect differences based on smoking status, age less than 55 years versus age 55 years and older, racial subgroups (White, Black, and Asian), or BMI subgroups.[6]

Recommendations:

- Add fezolinetant to the Preferred Drug List and designate as non-preferred with prior authorization (PA) criteria as presented in **Appendix 2**.
- Review costs in Executive Session.

Background:

Menopause is characterized by decreased ovarian estrogen secretion with corresponding cessation of the menstrual cycle and onset of vasomotor and vulvovaginal atrophy symptoms.[7] Menopause typically occurs between the age of 45 to 55 years, with a mean age of onset around 51 years.[4] Approximately 60% to 80% of women experience vasomotor symptoms, 20% of them are considered severe symptoms.[8] 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.[9] Hot flashes involve sudden sensations of heat in the upper body.[6] 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.[10] Vasomotor symptoms can persist on average of 7 to 10 years.[4] These symptoms can have a substantial negative impact on quality of life, contributing to physical and psychosocial impairment that can affect work performance, social activities, and personal and social relationships.[9]

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.[8] In all racial/ethnic groups, vasomotor symptom reports increase as women progress from premenopause to early perimenopause and even more dramatically as they make the transition to late perimenopause.[8] Other risk factors related to severity of vasomotor symptoms include older age, body mass index greater than 30 kg/m^2, 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.[8]

Guidance from the 2022 position statement of the North American Menopause Society considers estrogen products (oral, topical or vaginal) the most effective treatment for bothersome vasomotor symptoms and should be considered in women who need additional treatment for menopausal symptoms who do not have contraindications to estrogen therapy.[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.[6] Estrogen therapy is FDA approved for 4 indications: moderate to severe vasomotor symptoms; prevention of osteoporosis in postmenopausal women; treatment of hypoestrogenism caused by hypogonadism; and treatment of moderate to severe vulvovaginal symptoms.[11] 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]

For women who cannot tolerate progestin therapy due to breast tenderness or vaginal bleeding, bazedoxifene 20 mg is an alternative treatment. Bazedoxifene is a selective estrogen-receptor modulator (SERM) and is combined with conjugated estrogen 0.45 mg to form a tissue selective estrogen complex to provide endometrial protection without the need for progestins.[11] The combination of bazedoxifene/conjugated estrogen (DUAVEE) is FDA-approved for managing vasomotor symptoms associated with menopause and to prevent postmenopausal osteoporosis.[14] Like other SERMs, the risk of VTE is increased with bazedoxifene.[14] The combination of conjugated estrogen 0.45 mg/bazedoxifene 20 mg in women with moderate to severe hot flashes decreases hot flash frequency by approximately 75 percent (versus 50 percent for placebo).[15]

The selective serotonin reuptake inhibitor (SSRI) paroxetine (BRISDELLE) 7.5 mg, is a non-hormonal product FDA-approved to treat moderate to severe vasomotor symptoms associated with menopause.[16] Low-dose paroxetine has reduced the frequency and severity of hot flashes by approximately 40% to 65% compared to placebo at 4 weeks, but it can cause headache, lethargy, nausea, and vomiting.[13,16] There are no comparative trials that have evaluated efficacy of other paroxetine formulations or other antidepressants for treatment of vasomotor symptoms. Paroxetine can interfere with conversion of tamoxifen to its active metabolite, so it should not be used in women who are taking tamoxifen.[16] This SSRI formulation is not indicated for treatment of any psychiatric condition.[16]

Other non-hormone therapies to relieve vasomotor symptoms have been studied using selective neurokinin 3 receptor antagonists. The origin of hot flashes is in the thermoregulatory center of the hypothalamus.[17] This area of the brain is innervated by kisspeptin, neurokinin B, dynorphin (KNDy) neurons.[17] The KNDy neurons are stimulated by neurokinin B, acting at the neurokinin 3 receptors, and are inhibited by estrogen.[17] When estrogen levels decline with the menopause transition, neurokinin 3 receptor-mediated activation is then unopposed in the absence of estrogen.[17] This leads to the hypertrophy of the KNDy neurons and alters the activity of the thermoregulatory center, resulting in hot flashes.[17] Fezolinetant acts as a selective neurokinin 3 receptor antagonist, resulting in reduced episodes of hot flashes.[17] More details regarding the safety and efficacy of fezolinetant are discussed in the clinical summary below.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Fezolinetant (VEOZAH), received FDA-approval May 2023 for the treatment of moderate-to-severe vasomotor symptoms associated with menopause in people assigned female at birth.[1] The recommended dose is 45 mg orally once daily with or without food.[1] Two phase 3 clinical trials, Skylight 1 and Skylight 2, contribute to the efficacy data for reduction of vasomotor symptoms, which are described and evaluated below in **Table 3**.

In Skylight 1[3] and Skylight 2,[2] 1022 postmenopausal participants aged 40 to 65 years (522 in Skylight 1 and 500 in Skylight 2) who had a minimum average of 7 moderate-to-severe vasomotor symptoms per day were randomized to fezolinetant 30 mg, 45 mg, or placebo.[1] Both trials were conducted in the United States, Canada and Europe.[6] Randomization was stratified by smoking status (nonsmoker/former smoker and current smoker).[1] The mean age of the participants enrolled in the 2 studies was 54 years.[1] Participants self-identified as White (81%), Black (17%), Asian (1%), and Hispanic ethnicity (24%).[1] The study population included menopausal participants with one or more of the following: prior hysterectomy (32.1%), prior oophorectomy (21.6%), or prior hormone therapy use (19.9%).[1] Those who were on prior hormone therapy underwent a wash-out period prior to trial participation.[1]

The 2 trials included a 12-week, double-blind, placebo-controlled period followed by a 40-week, double-blind, extension period of fezolinetant exposure only (52-weeks in total).[6] The co-primary efficacy endpoints for both trials were the mean change from baseline in moderate-to-severe vasomotor symptom frequency per day (≥ 2 hot flashes over 24 hours considered clinically significant) and change from baseline in symptom severity to Weeks 4 and 12.[1] Severity of vasomotor symptoms was defined as mild (sensation of heat without sweating), moderate (sensation of heat with sweating but able to continue activity) or severe (sensation of heat with sweating causing cessation of activity).[4] Severity of score for mild, moderate and severe vasomotor symptoms was coded as 1,2, and 3, respectively.[4] Participants recorded changes in frequency and severity of symptoms daily in an electronic diary. Participants had to provide data for 50% of any given week (≥4 days) for their data to be included in the analysis.[2] The trial designs were consistent with FDA Guidance for Industry focused on "Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms".[4]

The mean baseline frequency of vasomotor symptoms in Skylight 1 ranged from 10.4 to 10.7 symptoms per day across the 3 treatment groups.[3] In Skylight 2, the mean baseline frequency of vasomotor symptoms ranged from 11.23 to 11.79 symptoms per day.[2] In both trials, only the 45 mg dose met the clinical threshold of superiority in frequency reduction by at least 2 hot flashes per day when compared to placebo at Weeks 4 and 12.[4] Moderate-quality evidence showed a statistically significant reduction from baseline in vasomotor symptom frequency with fezolinetant 45 mg versus placebo in Skylight 1 and Skylight 2 at week 4 (LSM difference: −2.07 and −2.55, respectively; $p<0.01$) and week 12 (LSM difference: −2.55 and −2.53, respectively; $p<0.01$).[2,3]

Mean symptom baseline severity scores in Skylight 1 ranged from 2.39 to 2.43 across all 3 treatment groups.[6] In Skylight 2, the mean baseline symptom severity scores ranged from 2.41 to 2.44.[2] Reductions in symptom severity were reduced in fezolinetant 45 mg recipients compared to placebo recipients at Week 4 (LSM difference −0.19 and −0.29; p<0.01) and Week 12 (LSM difference: −0.20 and −0.29; p<0.01; moderate-quality evidence for both endpoints).[2,3] The manufacturer only requested approval for the 45 mg daily dose.[4]

A secondary endpoint was mean change in the Patient-Reported Outcomes Measurement Information System Sleep Disturbance—Short Form 8b (PROMIS SD SF 8b) total score from baseline to week 12.[2] PROMIS SD SF 8b assesses self-reported sleep disturbance during the prior 7 days and includes perceptions of restless sleep; satisfaction with sleep; refreshing sleep; difficulties sleeping, getting to sleep, or staying asleep; amount of sleep; and sleep quality.[2] Responses to the 8 items range from 1 to 5, and the range of possible summed raw scores is 8 to 40. Higher scores on PROMIS SD SF 8b indicate more disturbed sleep.[2] Participants completed the PROMIS SD SF 8b electronically via a tablet at each site visit (every 4 weeks).[2] Moderate-quality evidence showed the mean change from baseline to week 4 and week 12 in sleep disturbance score was not significant in Skyline 1 (-0.5 and -1.1, respectively; p>0.05).[3] Of note, disturbed sleep was not a prerequisite for study inclusion, which could affect these results.[3] In Skylight 2, improvement in sleep score at week 12 was statistically significant for fezolinetant 45 mg (LSM difference, −2.0; 95% CI −3.5 to −0.6; p=0.007), but not for fezolinetant 30 mg (LSM difference, −0.7; 95% CI −2.1 to 0.8; p=0.381).[2]

There were several limitations of these studies. First, is absence of placebo comparison beyond 12 weeks. Additionally, other menopause symptoms, such as mood changes and sexual function, were not assessed. Most of the postmenopausal women enrolled in the clinical trials were White (80%), although observational studies have indicated that Black and Hispanic women experience higher frequency and severity of vasomotor symptoms.[8] All of the women enrolled in the studies were healthy, between the ages of 40 and 65 years, and with a body mass index (BMI) less than 39 kg/m^2. More data is needed to evaluate safety and efficacy in women over the age of 65 years and with co-morbidities including renal impairment. Finally, in these studies, the frequency and severity of vasomotor symptoms were also reduced in the placebo group indicating a placebo effect.[3] A strong placebo effect is widely reported in studies investigating potential treatments for vasomotor symptoms.[3] Trials in which the efficacy of SSRI's or hormone replacement therapy in reducing frequency and severity of vasomotor symptoms compared to neurokinin 3 receptor antagonists have not been conducted. Evidence from comparative trials would provide context for the place in therapy of fezolinetant to manage bothersome vasomotor symptoms associated with menopause.

Clinical Safety:
The primary endpoints for the randomized, double-blind, 52-week, phase 3 safety study, SKYLIGHT 4, included TEAEs and the percentage of women with endometrial hyperplasia or endometrial malignancy associated with fezolinetant 30 mg and 45 mg.[5] A total of 1,830 postmenopausal women were randomized equally to receive placebo, fezolinetant 30 mg or 45 mg.[5] In the placebo group 64% (n=391) TEAEs were reported, compared with 68% (n=415) in 30-mg group, and 64% (n=389) of the fezolinetant 45-mg group.[5] There was one occurrence of endometrial hyperplasia in the fezolinetant 45 mg group and none in the placebo or the fezolinetant 30 mg group.[5] There was one case of endometrial cancer in the fezolinetant 30 mg group and none in the placebo or fezolinetant 45 mg group.[5] Uterine bleeding occurred in 4.9% of patients in the placebo group, 3.3% of those in the fezolinetant 30 mg group, and 3.1% of those in the fezolinetant 45 mg group.[5]

The adverse reactions reported in at least 2% of patients treated with fezolinetant 45 mg and greater than placebo in Skylight 4 are presented in **Table 1**.[1] Hepatic transaminase elevations greater than 3 times the ULN were observed that were approximately 2-fold greater in 45 mg fezolinetant-treated patients compared with placebo-treated patients.[6] These hepatic transaminase elevations occurred at various timepoints in the 12-month clinical trials, were generally transient, and resolved while on fezolinetant 45 mg or shortly after discontinuation.[6]

Table 1. Adverse Reactions Reported In At Least 2% Of Fezolinetant-Treated Patients Compared With Placebo in Skylight 4[1]

Adverse Reaction	Fezolinetant 45 mg N = 609	Placebo N = 610
Abdominal Pain	26 (4.3%)	13 (2.1%)
Diarrhea	24 (3.9%)	16 (2.6%)
Insomnia	24 (3.9%)	11 (1.8%)
Back Pain	18 (3.0%)	13 (2.1%)
Hot Flush	15 (2.5%)	10 (1.6%)
Hepatic Transaminase Elevation	14 (2.3%)	5 (0.8%)

Fezolinetant is a substrate of CYP1A2 and concomitant use of fezolinetant with CYP1A2 inhibitors (e.g., cimetidine, amiodarone, mexiletine, ciprofloxacin, fluvoxamine) increased the plasma concentration of fezolinetant.[1] Fezolinetant is contraindicated in patients using CYP1A2 inhibitors, with estimated glomerular filtration rate (eGFR) less than 30 mL/min, and in patients with Child-Pugh Class C cirrhosis.[1] Assessing hepatic function, including serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin (total and direct) is recommended at baseline, in addition to monitoring these parameters at 3, 6 and 9 months after initiating treatment and when symptoms suggest liver injury.[1]

Look-alike / Sound-alike Error Risk Potential: No results available

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Change from baseline in severity of moderate to severe vasomotor symptoms
2) Decrease in frequency of hot flashes (at least 2 hot flashes per day or 14 per week)
3) Serious adverse events
5) Study withdrawal due to an adverse event

Co-Primary Study Endpoints:

1) Mean daily change from baseline to Weeks 4 and 12 in vasomotor frequency and severity

Table 2. Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Neurokinin 3 receptor antagonist which blocks neurokinin B binding on neurons that modulate activity in the thermoregulatory center.
Oral Bioavailability	Median time to reach Cmax is 1.5 hrs.
Distribution and Protein Binding	Volume of distribution is 189 L. Plasma protein binding is 51%.
Elimination	Clearance rate is 10.8 L/hr. 77% is excreted in the urine and 15% is excreted in the feces (unchanged).
Half-Life	9.6 hours in women with vasomotor symptoms.
Metabolism	Primarily metabolized by CYP1A2 and to a lesser extent by CYP2C9 and CYP2C19.

Abbreviations: Cmax = maximum concentration; hrs = hours; L= liters

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Lederman S., et al.[3] Skylight 1 DB, MC, 12-week PC followed by NC 40-week period Phase 3 RCT	1. Fezolinetant 30 mg orally once a day for 12 weeks 2. Fezolinetant 45 mg orally once a day for 12 weeks 3. Placebo tablet orally once a day for 12 weeks	Demographics: -Mean age: 54 yo -Mean BMI: 28 kg/m^2 -Race Native American: 2% Asian: 2% Black: 14% White: 82% -Ethnicity: Hispanic: 26% -Time since onset of VMS: 6-7 yrs -Baseline VMS frequency: 10-11 symptoms/day -Active smoker: 13% -Hysterectomy: 33% -Oophorectomy: 21% -Previous HRT therapy: 20% Key Inclusion Criteria: -Assigned female at birth, aged 40 to 65 yo with moderate-to-severe VMS associated with menopause -Amenorrhea for ≥ 12 mos or amenorrhea for ≥ 6 mos with FSH > 40 IU/L or bilateral oophorectomy ≥ 6 weeks prior to screening - ≥ 7 hot flashes per day within 10 days prior to randomization -BMI 18 to 38 kg/m^2 Key Exclusion Criteria: -Receiving strong or moderate CYP1A2 inhibitors, hormone	ITT: 1. 173 2. 174 3. 175 PP: 1. 143 2. 160 3. 152 Attrition: 1. 31 (18%) 2. 13 (7%) 3. 23 (13%)	4 Co-Primary Endpoints: 1. LSM change from baseline in frequency of moderate-to-severe VMS at Week 4 1. -5.19 2. -5.39 3. -3.32 Difference 1 vs 3: -1.87 95% CI -2.69 to -1.05 P<0.001 2 vs 3: -2.07 95% CI -2.89 to -1.25 P<0.001 2. LSM change from baseline in frequency of moderate-to-severe VMS at Week 12 1. -6.28 2. -6.44 3. -3.90 Difference 1 vs 3: -2.39 95% CI –3.25 to -1.52 P<0.001 2 vs 3: -2.55 95% CI -3.40 to -1.70 P<0.001 3.LSM change from baseline in severity of moderate-to-severe VMS at Week 4 (Scale 1-3) 1. -0.42 2. -0.46 3. -0.27 Difference 1 vs 3: -0.15	NA NA NA NA	TEAEs at 12 weeks 1. 65 (37%) 2. 75 (43%) 3. 78 (45%) SAEs at 12 weeks 1. 2 (1%) 2. 2 (1%) 3. 1 (1%) TEAEs leading to drug discontinuation at 12 weeks 1. 10 (6%) 2. 4 (2%) 3. 9 (5%) Elevated LFTs at 12 weeks 1. 6 (3%) 2. 7 (4%) 3. 5 (3%) 95% CI and p-values not reported	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomized 1:1:1 using web based IRT and stratified by active smoker vs. never/former smoker status. Baseline characteristics similar between groups. Performance Bias: Low. Fezolinetant tablets had the same appearance and shape as placebo tablets. Investigators, project team members, clinical staff and participants blinded to treatment assignment during 12-week PC phase. Blinding assigned and managed by IRT. Investigators and participants blinded during 40-week extension phase. Detection Bias: High. VMS recorded daily in an electronic diary by participants. Placebo effect may have biased VMS reporting. Participants had to provide data for 50% of any given week (≥4 days) for their data to be included in the analysis. Attrition Bias: High. Attrition rates varied amongst the 3 groups and were greater than 10%. Primary reasons for discontinuation were adverse events and study withdrawal. Missing data were imputed assuming treatment benefits diminished after discontinuing treatment. Reporting Bias: Low. Protocol available online. All outcomes reported as prespecified. Other Bias: High. Funded by manufacturer. Manufacturer's employees contributed to study design, data analysis, and drafted the manuscript for publication. **Applicability**: Patient: Most of the enrolled participants were white, while observational studies have shown that Black and Hispanic women have a higher incidence of VMS. Enrolled population reflects Oregon Medicaid, but more diverse enrollment would provide broader

		replacement therapy, hormonal contraception, or any treatment for VMS -SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg based on 2-3 readings during screening -History of undiagnosed uterine bleeding -Active liver disease, elevated LFTs, or eGFR ≤ 59 mL/min -Chronic neurologic, cardiovascular, gastrointestinal, pulmonary, or endocrine disease		95% CI -0.27 to -0.03 P=0.012 2 vs 3: -0.19 95% CI -0.30 to -0.7 P=0.002 4. LSM change from baseline in severity of moderate-to-severe VMS at Week 12 (Scale 1-3) 1. -0.60 2. -0.57 3. -0.37 Difference 1 vs 3: -0.24 95% CI -0.39 to -0.09 P=0.002 2 vs 3: -0.20 95% CI -0.35 to -0.06 P=0.007 Secondary Endpoint: Mean change in patient reported sleep disturbance (PROMIS SD SF 8b) score from baseline to week 12 1. -3.2 2. -3.7 3. -4.2 Difference 1 vs 3: -0.5 p=0.49 2 vs 3: -1.1 p=0.16	NA NA NA NS NS			applicability for this drug. Study results are limited to women aged 40 to 65 yo with a BMI < 38 kg/m^2. More data is needed to evaluate safety and efficacy in women over 65 yo with moderate renal impairment. Intervention: Fezolinetant dosing established in Phase 2 dose ranging clinical trials that assessed 15, 30, 50, and 90 mg dosing twice daily or 30, 60, and 120 mg once daily. Comparator: Placebo is an appropriate comparator in trials of a new drug with a novel mechanism. Comparative studies with hormone replacement therapy or paroxetine 7.5 mg would provide more evidence regarding efficacy. Outcomes: Change in frequency and severity of VMS were appropriate efficacy measures. Efficacy evaluated over 12 weeks. Longer duration of placebo-controlled phase would provide long term data regarding efficacy. Setting: 97 sites in the United States, Canada, United Kingdom, Spain, Poland, Czech Republic, and Hungary
2. Johnson KA, et al.[2] Skylight 2 MC, DB, 12-week PC followed by NC 40-week	1. Fezolinetant 30 mg orally once a day 2. Fezolinetant 45 mg orally once a day	Demographics: -Mean age: 54 yo -Mean BMI: 28 kg/m^2 -Race Native American: <1% Asian: <1% Black: 20% White: 79% -Ethnicity: Hispanic: 21%	ITT: 1. 166 2. 167 3. 167 PP: 1. 152 2. 155 3. 151	Co-Primary Endpoints: 1. LSM change in frequency of moderate-to-severe VMS from baseline to week 4 1. -5.52 2. -6.24 3. -3.64 Difference 1 vs 3: -1.82	NA	TEAEs at 12 weeks 1. 67 (40%) 2. 60 (36%) 3. 54 (32%) SAEs at 12 weeks 1. 3 (1.8%) 2. 2 (1.2%) 3. 0	NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: See Skylight 1 Performance Bias: See Skylight 1. Detection Bias: see Skylight 1. Attrition Bias: Low. Similar attrition rates across all 3 groups. Attrition less than 10% in all 3 groups. Reporting Bias: see Skylight 1. Other Bias: See Skylight 1.

period Phase 3 RCT	3. Placebo tablet orally once a day.	- Time since onset of VMS: 6.5-7 yrs - Active smoker: 21% -Hysterectomy: 30% -Oophorectomy: 21% -Previous HRT therapy: 20% Key Inclusion Criteria: see Skylight 1 Key Exclusion Criteria: see Skylight 1	Attrition: 1. 14 (8.4%) 2. 12 (7.2%) 3. 16 (9.6%)	95% CI -2.73 to -0.91 P<0.001 2 vs 3: -2.55 95% CI -3.45 to -1.64 P<0.001 2. LSM change in frequency of moderate-to-severe VMS from baseline to week 12 1. -6.43 2. -7.43 3. -4.57 Difference 1 vs 3: -1.86 95% CI -2.94 to -0.78 P<0.001 2 vs 3: -2.53 95% CI -3.60 to -1.46 P<0.001 3. LSM change in severity of moderate-to-severe VMS from baseline to week 4 (Scale 1 to 3) 1. -0.47 2. -0.61 3. -0.31 Difference 1 vs 3: -0.15 95% CI -0.27 to -0.02 P=0.021 2 vs 3: -0.29 95% CI -0.41 to -0.16 P<0.001 4. LSM change in severity of moderate-to-severe VMS from baseline to week 12 (Scale 1-3) 1. -0.60 2. -0.74 3. -0.46 Difference	NA NA NA	TEAEs leading to drug discontinuation at 12 weeks 1. 1 (0.6%) 2. 5 (3.0%) 3. 1 (0.6%) Elevated LFTs at 12 weeks 1. 2 (1.2%) 2. 3 (1.8%) 3. 0 95% CI and p-values not reported	NA NA	**Applicability**: Patient: See Skylight 1. Intervention: See Skylight 1. Comparator: See Skylight 1. Outcomes: See Skylight 1. Setting: 146 sites in United States, Canada, United Kingdom, Spain, Poland, Czech Republic, and Latvia

				1 vs 3: -0.16 95% CI -0.33 to 0.00 P=0.49 2 vs 3: -0.29 95% CI -0.45 to -0.13 P<0.001 <u>Secondary Endpoint:</u> LSM change in patient reported sleep disturbance (PROMIS SD SF 8b) score from baseline to week 12 1. -4.1 2. -5.5 3. -3.4 Difference 1 vs 3: -0.7 95% CI -2.1 to 0.8 P=0.381 2 vs 3: -2.0 95% CI -3.5 to -0.6 P=0.007	NS NA			
3.Neal-Perry G, et al.[5] SKYLIGHT 4 DB, PC, Phase 3 RCT over 52 weeks	1. Fezolinetant 30 mg orally once a day 2. Fezolinetant 45 mg orally once a day 3. Placebo tablet orally once a day.	<u>Demographics</u>: -Mean age: 54 yo -Mean BMI: 28 kg/m^2 -Race Native American: <1% Asian: 1.5% Black: 17% White: 81% -Ethnicity Hispanic: 20% -Active smoker: 19% -Hysterectomy: 19% -Oophorectomy: 13% -Previous HRT therapy: 17% <u>Key Inclusion Criteria</u>: -See Skylight 1 <u>Key Exclusion Criteria</u>: -See Skylight 1	<u>ITT</u>: 1. 611 2. 609 3. 611 <u>PP</u>: 1. 451 2. 444 3. 410 <u>Attrition</u>: 1. 79 (13%) 2. 85 (14%) 3. 119 (14%)	<u>Primary Endpoints</u> 1. TEAEs at 52 weeks 1. 415 (68%) 2. 389 (64%) 3. 391 (64%) 95% CI and p-values not reported 2. Percentage of participants with endometrial hyperplasia (95% CI) 1. 0 (0 to 1.4) 2. 1 (0.5 to 2.3) 3. 0 (0 to 1.6) 3. Percentage of participants with endometrial malignancy (95% CI) 1. 1 (0.5 to 2.2) 2. 0 (0 to 1.5)		<u>SAEs</u> 1. 20 (3.3%) 2. 23 (3.8%) 3. 14 (2.3%) <u>TEAEs leading to drug discontinuation</u> 1. 34 (5.6%) 2. 28 (4.6%) 3. 26 (4.3%) <u>Elevated LFTs (3 x's ULN)</u> 1. 8 (1.4%) 2. 12 (2.0%) 3. 6 (1.0%)		**Risk of Bias (low/high/unclear)**: <u>Selection Bias</u>: See Skylight 1. <u>Performance Bias</u>: See Skylight 1. <u>Detection Bias</u>: See Skylight 1. <u>Attrition Bias</u>: Low. Attrition rates were similar and less than 20%. <u>Reporting Bias</u>: See Skylight 1. <u>Other Bias:</u> See Skylight 1. **Applicability**: <u>Patient</u>: See Skylight 1. <u>Intervention</u>: Doses used in the safety analysis were studied in 2 other phase 3 RCTs. <u>Comparator</u>: Placebo is an appropriate comparator for the safety analysis. <u>Outcomes</u>: TEAEs and impact on endometrial tissue are appropriate safety concerns with this drug. <u>Setting</u>: 182 sites in United States, Canada, United Kingdom, Czech Republic, Poland, Ukraine, Latvia

				3. 0 (0 to 1.6)				

Abbreviations: ARR = absolute risk reduction; BMI = body mass index; CI = confidence interval; DB = double-blind; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; HRT = hormone replacement therapy; IRT = Interactive Response Technology; ITT = intention to treat; IU = International Units; LFTs= liver function tests; LSM = least squares mean; mITT = modified intention to treat; MC = multi-center; mos = months; N = number of subjects; NC = non-controlled; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported: PC = placebo-controlled; PP = per protocol; PROMIS SD SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance-Short Form 8b; RCT = randomized controlled trial; SBP = systolic blood pressure; SAEs = serious adverse effects; TEAEs = treatment-emergent adverse events; ULN = upper limit of normal; VMS = vasomotor symptoms; yo = years old.

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VEOZAH safely and effectively. See full prescribing information for VEOZAH.

VEOZAH™ (fezolinetant) tablets, for oral use
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

VEOZAH is a neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms due to menopause. (1)

DOSAGE AND ADMINISTRATION

Perform baseline bloodwork to evaluate for hepatic function and injury before beginning VEOZAH. While using VEOZAH, perform follow-up bloodwork at 3 months, 6 months, and 9 months after initiation of therapy and when symptoms suggest liver injury.

One 45 mg tablet orally once daily with or without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 45 mg (3)

CONTRAINDICATIONS

- Known cirrhosis (4, 5.1)
- Severe renal impairment or end-stage renal disease (4, 8.6)
- Concomitant use with CYP1A2 inhibitors (4, 7.1)

WARNINGS AND PRECAUTIONS

Hepatic transaminase elevation: Elevations in serum transaminase concentrations greater than three times the upper limit of normal (ULN) occurred in the clinical trials. Perform bloodwork prior to initiation of VEOZAH to evaluate for hepatic function and injury. Do not start therapy if serum transaminase concentration is equal to or exceeds two times the ULN. Perform follow-up evaluations of hepatic transaminase concentration at 3 months, 6 months, and 9 months after initiation of therapy. (5.1)

ADVERSE REACTIONS

The most common adverse reactions with VEOZAH [at least 2% in VEOZAH 45 mg and greater than placebo] are: abdominal pain, diarrhea, insomnia, back pain, hot flush, and hepatic transaminase elevation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Approved: 5/2023

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?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request to treat vasomotor symptoms in a post-menopausal person?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Does the patient have intolerance or contraindications to hormone replacement therapy (e.g., estrogen/progestin)?	**Yes:** Go to # 4	**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. 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 #6
6. Is the estimated glomerular filtration rate (eGFR) < 30 mL/min?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #7
7. Have baseline liver function tests (LFTs) been obtained?	**Yes:** Go to #8 and document baseline labs_____	**No:** Pass to RPh. Deny; medical appropriateness.
8. Do LFTs indicate presence of severe cirrhosis (i.e., serum transaminase concentrations greater than 2 times the upper limit of normal)?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for 6 months.

Renewal Criteria		
1. Have frequency and severity of vasomotor symptoms been reduced with fezolinetant treatment?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness.
2. Have liver function tests (LFTs) been requested at 3- and 6-month intervals 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 greater than 2 times the upper limit of normal)?	**Yes**: Pass to RPh. Deny; medical appropriateness.	**No:** Approve for 12 months**.**