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New Drug Evaluation: Lynkuet® (elinzanetant), capsules

Date of Review: April 2026
Generic Name: Elinzanetant

End Date of Literature Search: 12/10/2025
Brand Name (Manufacturer): LYNKUET (Bayer)
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. These symptoms can be severe enough to interrupt sleep or cause anxiety and depression in some women.
- Hormone therapy with medications that contain estrogen or progesterone can be prescribed to reduce how often hot flashes occur and how severe they feel. However, estrogens when taken without progesterone can increase the risk of uterine cancers. People that have a uterus often take estrogen with progesterone to alleviate the risk of uterine cancer.
- A new medicine, LYNKUET (elinzanetant), was approved by the Food and Drug Administration (FDA) to treat hot flashes due to menopause. It is similar to fezolinetant, which has been available for a few years. These medicines are not hormone therapy. Neither medicine is a hormone, like estrogen or progesterone.
- This review looked at the evidence for how well elinzanetant works and the side effects caused by this medicine. Two studies found that the amount and the severity of hot flashes were reduced in post-menopausal women who received elinzanetant 120 mg once a day.
- Side effects reported with elinzanetant included headache, feeling tired or drowsy, dizziness, stomach pain, rash, muscle spasm, and diarrhea. It is unclear if the medicine affects the liver, so blood work should be done to check liver function tests before and once after starting treatment.
- Hormone therapy is covered by the Oregon Health Plan's fee-for-service program. Prior authorization must be submitted by the prescriber before elinzanetant can be covered.

Research Questions:

1. What is the efficacy of elinzanetant in reducing the frequency of moderate-to-severe vasomotor symptoms associated with menopause?
2. What are the harms of elinzanetant when used to reduce vasomotor symptoms associated with menopause?
3. Does elinzanetant differ in effectiveness or harms based on specific demographic characteristics (e.g., smoking status, age, race, ethnicity)?

Conclusions:

- The dual neurokinin-1 and neruokin-3 receptor antagonist LYNKUET (elinzanetant) received FDA approval October 2025 for the treatment of moderate-to-severe vasomotor symptoms associated with menopause.[1] Two, phase 3, randomized controlled trials (RCTs), OASIS 1 and OASIS 2,[2] contribute to the efficacy data for this indication and are evaluated in **Table 3.** In these identically designed trials, a total of 796 of postmenopausal patients identified as

women at birth aged 45 years to 60 years who had an average of 50 moderate to severe vasomotor symptoms per week were randomized to elinzanetant 120 mg or placebo once a day for 12 weeks.[2]

- The co-primary endpoints studied in both trials were least-square mean (LSM) change in frequency (a reduction of at least 2 vasomotor events per day is considered clinically significant) and change in severity of moderate-to-severe vasomotor symptoms at Weeks 4 and 12 (a 50% reduction in severity is considered clinically significant).[2] Frequency and severity of vasomotor symptoms was defined as mild, moderate, or severe and recorded in an electronic diary twice daily by study participants.[2] The results are summarized in **Table 1**. These two trials provide moderate-quality evidence that elinzanetant provides statistically significant reductions in vasomotor symptom frequency and severity for up to 12 weeks.[2]
- In OASIS 1 and 2, commonly reported adverse effects through the first 12 weeks of treatment included headache, fatigue, gastroesophageal disease, dizziness, nausea and somnolence.[1] Similar adverse events were reported in the 52-week Oasis 3 trial and are presented in **Table 2** below.
- Concomitant use of elinzanetant should be avoided with strong CYP3A4 inhibitors, grapefruit juice, strong CYP3A4 inducers, and moderate CYP3A4 inducers.[1] When co-administered with moderate CYP3A4 inhibitors, the dose of elinzanetant should be reduced to 60 mg once a day.[1] Based on findings from animal studies, elinzanetant may cause pregnancy loss or stillbirth.[1] For this reason, elinzanetant is contraindicated in pregnancy.[1]
- Elevations in serum transaminase (alanine transaminase [ALT] and/or aspartate aminotransferase [AST]) concentrations equal to or greater than three times the upper limit of normal (ULN) occurred in 0.6% of patients receiving elinzanetant and 0.4% of patients receiving placebo up to 12 weeks in the 3 clinical trials.[1] For this reason, the FDA labeling recommends obtaining baseline bloodwork (including ALT, AST, alkaline phosphatase, and total and direct bilirubin) prior to initiation.[1] Therapy should not be started if serum transaminase concentration is equal to or exceeds two times the upper limit of normal (ULN) or if the total bilirubin is equal to or exceeds two times the ULN.[1] Follow-up evaluations of hepatic transaminase concentrations should be performed 3 months after initiation of therapy.[1] Long-term studies will provide more data on the risks of elinzanetant-induced hepatic injury.
- Elinzanetant has been studied in women with moderate to severe vasomotor symptoms who were receiving endocrine therapy (tamoxifen or aromatase inhibitors) for hormone receptor-positive breast cancer (n = 474).[3] In this trial, elinzanetant-treated patients experienced statistically significant reductions in frequency of vasomotor symptoms compared to placebo-treated patients.[3] Use in this patient population is not yet FDA-approved.
- There is insufficient evidence to assess if elinzanetant differs in effectiveness or harms for any other patient-specific factors like smoking status, age, race, or ethnicity.

Recommendations:

- Create a PDL class called “Neurokinin Receptor Antagonists” and include both fezolinetant and elinzanetant in this class.
- Designate elinzanetant as non-preferred on the Preferred Drug List (PDL) with prior authorization (PA) criteria as presented in **Appendix 2**.

Background:

Menopause is characterized by decreased ovarian estrogen secretion with corresponding cessation of the menstrual cycle and onset of vasomotor and vulvovaginal atrophy symptoms.[4] Menopause typically occurs between the age of 45 to 55 years, with a mean age of onset around 51 years.[5] As menopause progresses, approximately 60% to 80% of women experience vasomotor symptoms; 20% of them experience severe symptoms.[6] Hot flashes and night sweats are the primary vasomotor symptoms, which may also be associated with sleep and mood disturbances, as well as decreased cognitive function.[7] Hot flash episodes usually last 1 to 5 minutes and are characterized by perspiration, flushing, chills, clamminess, anxiety, and on occasion, heart palpitations.[8] Vasomotor symptoms can persist for 7 to 10 years.[5] These symptoms can have a negative impact on quality of life, contributing to physical and psychosocial impairment that can affect work performance, social activities, and personal and social relationships.[7]

Prevalence of vasomotor symptoms varies between different racial and ethnic groups, with a higher incidence and longer duration of symptoms in Black and Hispanic women.[6] In all women, vasomotor symptoms increase as women progress from premenopause to early perimenopause and even more dramatically as they make the transition to late perimenopause.[6] Other risk factors related to severity of vasomotor symptoms include older age, body mass index greater than 30 kg/m^2, lack of college education, smoking history longer than 40 pack-years, and high baseline anxiety or depression scores.[6]

The American College of Obstetricians and Gynecologists (ACOG), North American Menopause Society (NAMS), and Endocrine Society recommend systemic menopausal hormone therapy – either estrogen combined with progestogen in patients with a uterus or estrogen alone in patient without a uterus – as first-line treatment for vasomotor symptoms of menopause.[9] The NAMS recommends oral or topical estrogen in women without contraindications who need additional treatment for menopausal symptoms.[10] Contraindications to estrogen include history of uterine cancer, hepatic disease or a venous thromboembolism event (VTE).[10] In addition, women over the age of 60 years 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.[10] In women with an intact uterus, estrogen is given in combination with a progestogen to prevent endometrial hyperplasia or carcinoma.[10]

Systemic estrogen alone or combined with a progestogen reduces the frequency of vasomotor symptoms by approximately 75% compared with placebo.[5] Vasomotor symptom reduction by 50% or greater is considered clinically meaningful.[10] 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.[10] Estrogen therapy is FDA approved for 4 indications: treatment of 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.[10]

Nonhormonal treatment options are also available to reduce vasomotor symptoms in those with contraindications to hormone therapy or who prefer not to receive hormone therapy. The 2023 NAMS position statement on nonhormonal therapy for management of menopausal symptoms recommends selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake Inhibitors (SNRIs), gabapentin, and oxybutynin for treatment of vasomotor symptoms.[9] All of the nonhormonal therapies are prescribed off-label but have evidence of efficacy at reducing severity or frequency of vasomotor symptoms, although their relative comparative evidence is insufficient.[9]

Selective neurokinin receptor antagonists are another class of nonhormonal therapies studied to relieve vasomotor symptoms. The origin of hot flashes is in the thermoregulatory center of the hypothalamus.[11] This area of the brain is innervated by kisspeptin/neurokinin B/dynorphin (KNDy) neurons.[11] The KNDy neurons are stimulated by neurokinin B, acting at the neurokinin 3 receptors, and are inhibited by estrogen.[11] When estrogen levels decline with the menopause transition, neurokinin 3 receptor-mediated activation is then unopposed in the absence of estrogen.[11] This leads to the hypertrophy of the KNDy neurons and alters the activity of the thermoregulatory center, resulting in hot flashes.[11]

Fezolinetant is a selective neurokinin 3 receptor antagonist indicated to reduce vasomotor symptoms associated with monopause.[11] Fezolinetant is also included in the NAMS position statement as an alternative to hormonal therapy for management of vasomotor symptoms (high-quality evidence).[9] The FDA has issued a black-boxed warning that fezolinetant can cause rare but serious liver injury based on a postmarketing case reports.[12]

Elinzanetant is a newly approved dual neurokinin-1 and neurokinin-3 receptor antagonist for management of vasomotor symptoms associated with menopause. It is pharmacologically similar to fezolinetant, which only inhibits neurokinin-3. The phase 3 RCTs assessed the impact of elinzanetant on the reducing the frequency and severity of hot flashes, improvements sleep disturbance and quality of life.

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of patient-centered instruments that evaluate physical, mental, and social health.[13] The validated PROMIS Sleep Disturbance Short Form 8b (PROMIS SD SF 8b) questionnaire is a short form derived from the 27-item PROMIS SD item bank.[14] The PROMIS SD SF 8b questionnaire assesses the degree of sleep disturbance over the past 7 days, with the 8 items particularly investigating restless sleep, satisfaction with sleep, refreshing sleep, difficulties falling asleep, staying asleep, getting to sleep, amount of sleep, and sleep quality.[14] Items are scored on a 5-point Likert scale, and the 8 single item scores are summed to yield total raw scores (range, 8-40), with higher scores indicating more disturbed sleep.[13] A change of 8 points or more in the PROMIS SD-SF-8b score is considered a clinically meaningful change in sleep disturbance.[13]

The 29-item Menopause Quality of Life (MENQOL) questionnaire assesses the presence of menopausal symptoms over the previous week.[15] Participants indicate whether or not they experienced a particular symptom and rate how bothersome it was on a 7-point scale (range, 0-6, with higher scores indicating the symptom is more bothersome).[15] The 29 items assess 4 domains of symptoms and functioning: vasomotor symptoms (items 1-3), psychosocial (items 4-10), physical (items 11-26), and sexual (items 27-29) domains.[15] Responses to single items are used to calculate 29 individual item scores. The 4 domain scores are calculated as a mean of converted single-item scores (range, 1-8, with higher scores indicating a higher degree of bothersome symptoms), and the mean of the 4 domain scores yield the MENQOL total score.[15] A change of 0.9 points represents a clinical meaningful difference.[2] Although health-related quality of life assessments such as the MENQOL questionnaire are useful for assessing the benefits of new treatments on menopause-related quality of life, demonstration of a statistical difference from placebo does not necessarily mean that improvements are clinically meaningful.[16] More details regarding the safety and efficacy of elinzanetant 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. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:
Elinzanetant received FDA approval for the treatment of moderate to severe vasomotor symptoms due to menopause.[1] The recommended dose is 120 mg (two 60 mg capsules) once daily at bedtime.[1] Two identically designed RCTs, OASIS 1 (n=396) and OASIS 2 (n=400), contribute to the short-term efficacy data for elinzanetant, which are described and evaluated in **Table 3**.

In the trials, women aged 40 to 65 years with moderate to severe menopausal vasomotor symptoms were randomized 1:1 to elinzanetant 120 mg or placebo once daily.[2] Postmenopausal status was defined as at least 12 months of spontaneous amenorrhea, or at least 6 months of spontaneous amenorrhea with serum follicle stimulating hormone levels greater than 40 mIU/mL and a serum estradiol concentration of less than 30 pg/mL, or at least 6 months after hysterectomy with serum follicle-stimulating hormone greater than 40 mIU/mL and serum estradiol less than 30 pg/mL, or at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy.[1] The study population included women with prior hysterectomy (38.8%), prior uni-/bilateral oophorectomy (20.6%), or prior menopausal hormone therapy use (31.4%).[1] For study enrollment, patients were required to have experienced at least 50 moderate to severe hot flashes per week.[1]

Participants in the elinzanetant arm received the active medication for 26 weeks, while patients in the placebo arm received placebo for 12 weeks and then switched to elinzanetant for the next 14 weeks. Co-primary end points included daily mean change in frequency and severity of vasomotor symptoms from baseline to weeks 4 and 12, as measured by an electronic hot flash diary that patients completed twice daily.[2] Possible ranges were 0 to 180 for the vasomotor symptom frequency score.[2] Mild hot flashes were defined as a sensation of heat without sweating (score of 1), moderate as a sensation of heat with sweating

but able to continue activity (score of 2), and severe as a sensation of heat with sweating that causes cessation of activity (score of 3).[2] In both trials, the week 4 and 12 endpoints also met clinically meaningful reduction in the frequency of moderate to severe hot flashes (≥2 hot flashes over 24 hours as presented in **Table 3**).[1] However, a clinically meaningful reduction with elinzanetant in the severity of vasomotor symptoms was not met. A reduction in 50% or more in the severity of vasomotor symptoms is considered a clinically meaningful effect.[10]

Secondary end points included effects on sleep disturbance (as measured by the PROMIS SD SF 8b total score) and quality of life (as measured by the MENQOL questionnaire total score) from baseline to week 12.[2] In both trials, the PROMIS SD SF 8b total score (range, 8 to 40) was converted to a total T-score to analyze this secondary endpoint (range 28.9 to 76.5).[2] A T-score of 50 represented the mean sleep disturbance score in a reference population.[2] T scores of 55 or greater, 60 or greater, and 70 or greater represented mild, moderate, and severe levels of sleep disturbances, respectively, in the reference population.[2] Both secondary endpoints showed statistically significant differences in favor of elinzanetant over placebo in the trials (**Table 3**).[17]

Trial Limitations

The OASIS 1 and 2 trials included only post-menopausal individuals.[18] Individuals experiencing vasomotor symptoms with perimenopause or due to endocrine therapy for breast cancer were not included.[18] Participants were primarily White, with 12% to 19% Black or African American and less than 10% Hispanic or Latino.[18] Other study limitations that may lead to certain biases include the subjective nature of how vasomotor symptoms present and the accuracy of recording each event, which may explain the strong placebo response in these trials.[18]

Long-Term Studies

The OASIS 3 (n=628) trial was a randomized, multi-center, multi-country, double-blind, placebo-controlled, parallel-group trial in which postmenopausal women aged 40 to 65 years were randomized 1:1 to receive either elinzanetant 120 mg daily or placebo for the full 52-week treatment period.[19] OASIS 3 was designed to provide long-term safety data at 52 weeks and supportive efficacy data at 12 weeks. Unlike the OASIS 1 and 2 trials, there was no requirement for a minimum number of vasomotor events per week. Baseline moderate to severe vasomotor event frequency was less than in OASIS 1 and 2 as women experienced a mean of 6.7 and 6.8 events per day (46 to 48 events per week) in the elinzanetant and placebo arms, respectively.[19] The primary efficacy endpoint for OASIS 3 was the mean change in the frequency of moderate to severe vasomotor symptoms as assessed by the patient-reported results in a daily hot flash diary from baseline to week 12.[19] At week 12, the LSM change from baseline in daily frequency of moderate to severe hot flashes was -5.4 for elinzanetant-treated patients and -3.5 for placebo-treated patients (difference, -1.6; 95% CI,- 2.0 to -1.1; p<0.001).[19] At baseline, the mean daily frequency of moderate to severe vasomotor symptoms was 11.4 episodes in the elinzanetant group and 11.5 episodes in the placebo–group.

In OASIS 4, women aged 18 to 70 years with moderate to severe vasomotor symptoms who were receiving endocrine therapy (tamoxifen or aromatase inhibitors) for hormone receptor-positive breast cancer (n = 474) were enrolled.[3] Patients were randomly assigned in a 2:1 ratio to receive elinzanetant 120 mg once a day for 52 weeks or placebo once daily for 12 weeks followed by elinzanetant 120 mg once a day for 40 weeks.[3] The primary end points were the LSM change in the mean daily frequency of moderate to severe vasomotor symptoms from baseline to week 4 and week 12.[3] At baseline, the mean daily frequency of moderate to severe vasomotor symptoms was 11.4 episodes in the elinzanetant group and 11.5 episodes in the placebo group.[3] At week 4, the LSM change from baseline was −6.5 episodes with elinzanetant and −3.0 episodes with placebo (difference, −3.5 episodes; 95% CI, −4.4 to −2.6; P<0.001).[3] At week 12, the LSM change was −7.8 episodes with elinzanetant and −4.2 episodes with placebo (difference, −3.4 episodes; 95% CI, −4.2 to −2.5; P<0.001).[3]

Clinical Safety:
In OASIS 1 and 2, commonly reported adverse effects through the first 12 weeks of treatment included headache, fatigue, gastroesophageal disease, dizziness, nausea and somnolence.[1] Similar adverse events were reported in the 52-week OASIS 3 trial. Ten cases of liver enzyme elevation occurred in the 52-week study, including 6 cases with elinzanetant; 5 cases were mild and one case was assessed as moderate.[19] These elevations were mostly asymptomatic and resolved in 5 of the 6 cases; the final case had an unknown outcome.[19] A summary of common adverse events reported in OASIS 3 is presented in **Table 2.**

Table 2. Adverse Events Reported in the OASIS 3 trial over 52 weeks[1]

Adverse Event	**Elinzanetant (n=313) N (%)**	**Placebo (n=314) N (%)**
Headache	30 (9.6)	22 (7.0)
Fatigue	23 (7.3)	9 (2.9)
Dizziness	19 (6.1)	6 9 (1.9)
Somnolence	16 (5.1)	4 (1.3)
Abdominal Pain	14 (4.5)	8 (2.5)
Rash	13 (4.2)	5 (1.6)
Diarrhea	12 (3.8)	3 (1.0)
Muscle Spasms	10 (3.2)	2 (0.6)

In OASIS-4 the most commonly reported adverse effects were headache, fatigue, and somnolence.[3] Serious adverse events occurred during weeks 1 through 12 in 8 participants (2.5%) receiving elinzanetant and 1 participant (0.6%) receiving placebo.[3] Elevations in liver-enzyme levels that were observed in 5 women, and all of these elevations occurred while the women were taking elinzanetant.[3] All cases were reversible and there did not appear to be a substantive hepatotoxicity signal with elinzanetant.[3]

Elinzanetant is primarily metabolized by the CYP3A4 hepatic enzyme and its metabolism can be impacted by co-administration with CYP3A4 inhibitors or inducers.[1] Concomitant use of elinzanetant should be avoided with strong CYP3A4 inhibitors, grapefruit juice, strong CYP3A4 inducers, and moderate CYP3A4 inducers.[1] When co-administered with moderate CYP3A4 inhibitors, the dose of elinzanetant should be reduced to 60 mg once a day.[1] Based on findings from animal studies, elinzanetant may cause pregnancy loss or stillbirth.[1]

Elevations in serum transaminase (ALT and/or AST) concentrations equal to or greater than three-times the ULN occurred in 0.6% of patients who received up to 12 weeks of elinzanetant and 0.4% of patients who received placebo in the OASIS 1, 2 and 3 trials.[1] For this reason, the manufacturer recommends obtaining baseline ALT, AST, alkaline phosphatase, and total and direct bilirubin prior to initiation of elinzanetant to evaluate hepatic function and risk for injury.[1] Therapy should not be started if serum transaminase concentrations are equal to or exceed 2-times the ULN or if the total bilirubin is equal to or exceeds 2 times the ULN.[1] Follow-up evaluations of hepatic transaminase concentration should be performed 3 months after initiation of therapy.[1] Elinzanetant is not recommended for use in patients with end stage renal disease with or without hemodialysis or in patients with moderate to severe hepatic impairment.[1]

Patients should be advised about the potential for somnolence and other central nervous effects when starting elinzanetant.[1] If patients experience drowsiness, they should refrain from driving or engaging in hazardous occupations until the effects have resolved.[1] In patients with a history of seizures, there is an increased risk of seizure activity with elinzanetant.[1]

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

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Decrease in frequency of vasomotor symptoms (at least 2 hot flashes per day or 14 per week)
2) Decrease in severity of vasomotor symptoms (scale of 0 to 3; at least 50% reduction from baseline)
3) Serious adverse events
4) Study withdrawal due to an adverse event

Co-Primary Study Endpoints:

1) LSM change in frequency and severity of vasomotor symptoms at weeks 4 and 12

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. Pinkerton, et al.[1,2] NCT05042362 OASIS 1 DB, MC, PC, Phase 3 RCT	1. Elinzanetant 120 mg PO QDay for 26 weeks 2. Placebo PO QDay for 12 weeks, followed by elinzanetant 120 mg for 14 weeks.	Demographics: -Mean age: 54.6 y -Race Asian: 1% Black: 19% White: 77% -Ethnicity: Hispanic: 8% -Baseline VMS per 24 hours Elinzanetant: 13.4 Placebo: 14.26 -Baseline VMS severity Elinzanetant: 2.56 Placebo: 2.53 -Baseline sleep disturbance score: 61 -Smoking history Elinzanetant: Never: 75% Former: 13% Current: 12% Placebo: Never: 58% Former: 17% Current: 25%	ITT: 1. 199 2. 197 PP: 1. 170 2. 65 Attrition 1. 29 (15%) 2. 32 (16%)	Primary Endpoints: LSM change in frequency of daily moderate to severe hot flashes from baseline to week 4. 1. -7.60 2. -4.31 Difference: -3.29 95% CI, -4.47 to -2.10; P<0.001 LSM change in frequency of moderate to severe hot flashes from baseline to week 12. 1. -8.66 2. -5.44 Difference: -3.22 95% CI, -4.81 to -1.63; P<0.001 LSM change in severity of moderate to severe hot flashes from baseline to week 4. 1. -0.73 2. -0.40 Difference: -0.33 95% CI, -0.44 to -0.23; P<0.001	NA NA NA	TEAEs over 12 weeks 1. n = 102 (51.3%) 2. n = 94 (48.5%) Study Discontinuation due to TEAEs at 12 weeks 1. n = 17 (8.5%) 2. n = 13 (6.7%) Serious TEAEs at 12 weeks 1. n = 4 (2%) 2. n = 2 (1%) Headache 1. n = 14 (7%) 2. n = 5 (2.6%) Fatigue 1. n = 14 (7%) 2. n = 3 (1.5%) Arthralgia 1. n = 10 (5%) 2. n = 10 (5.2%)		**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 1:1 via computer generated assignments. Baseline demographics were generally balanced between groups in both trials, except in smoking history. Unclear if smoking differences were due to poor randomization. Performance Bias: Low. Placebo was identical in appearance to active comparator. Patients, investigators, and outcome assessors blinded to treatment arm. Detection Bias: High. Patients documented frequency and severity of VMS via electronic hand-held device twice a day (morning and evening). Placebo effect may have biased VMS reporting in placebo-treated group. Attrition Bias: High. Dropout rate at 12 weeks was > 10%. Attrition due to adverse events, loss to follow up, and patient decision. Efficacy analysis completed on ITT population. Missing data imputed as last observation carried forward. Reporting Bias: Low. Trial protocol available online. All pre-specified primary and secondary outcomes reported. Other Bias: High. Study funded by the manufacturer. Several authors reported financial support from the manufacturer.

		Key Inclusion Criteria: -Postmenopausal females aged 40 to 65 y -Moderate to severe hot flashes and at least 50 over 7 days during screening. Key Exclusion Criteria: -Significant history of cardiac arrythmias -Uncontrolled or treatment-resistant hypertension -Untreated thyroid disease -Unexplained post-menopausal uterine bleeding -Abnormal liver function tests -Current or history of malignancy within the previous 5 years (except basal and squamous cell skin tumors)		LSM change in severity of moderate to severe hot flashes from baseline to week 12. 1. -0.92 2. -0.52 Difference: -0.40 95% CI -0.54 to -0.25; P<0.001 Secondary Endpoints: LSM change in sleep disturbance from baseline to week 12 as measured by the PROMIS SD SF 8b total t-score. 1. -10.8 2. -5.0 Difference: -5.6 95% CI -7.2 to -4; P<0.001 LSM change from baseline to week 12 in menopause quality of life as assessed by the MENQOL total score. 1. -1.41 2. -0.9 Difference: -0.4 95% CI -0.6 to -0.2; P<0.0001	NA NA NA	95% CI and p-values NR		**Applicability**: Patient: Most enrollees 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 applicability for this drug. Intervention: Four different doses of elinzanetant (40 mg, 80 mg, 120 mg and 160 mg per day) were evaluated in a Phase 2 RCT. 120 mg once daily was lowest most effective dose. No additional benefit was observed with the 160 mg dose. Comparator: Comparative trials with fezolinetant or hormone replacement therapy or would provide insight into the place of therapy for elinzanetant. Outcomes: Patient-reported reductions in frequency and severity of hot flashes are appropriate but long-term hepatic injury data will be instructive to prescribers. Setting: 77 locations in the United States, Austria, Czechia, Greece, Hungary, Israel, Italy, and the Netherlands.
2. Pinkerton, et al.[1,2] NCT05099159 OASIS 2 DB, MC, PC, Phase 3 RCT	1. Elinzanetant 120 mg PO QDay for 26 weeks 2. Placebo PO QDay for 12 weeks, followed by elinzanetant 120 mg for 14 weeks.	Demographics: -Mean age: 54.8 y -Race Asian: 0.5% Black: 15% White: 84% Hispanic: 8.5% -Ethnicity Hispanic: 9% -Baseline VMS per 24 hours Elinzanetant: 14.66 Placebo: 16.16 -Baseline VMS severity Elinzanetant: 2.53 Placebo: 2.54 -Baseline sleep disturbance score: 61 -Smoking history Elinzanetant:	ITT: 1. 200 2. 200 PP 1. 170 2. 179 Attrition 1. 30 (15%) 2. 21 (11%)	Primary Endpoints: LSM change in frequency of moderate to severe hot flashes from baseline to week 4. 1. -8.58 2. -5.54 Difference: -3.04 95% CI -4.40 to -1.68; P<0.001 LSM change in frequency of moderate to severe hot flashes from baseline to week 12. 1. -9.72 2. -6.48 Difference: -3.24 95% CI -4.60 to -1.88; P<0.001	NA NA	TEAEs over 12 weeks 1. n = 89 (44.3%) 2.n = 76 (38.2%) Study Discontinuation due to TEAEs at 12 weeks 1. n = 13 (6.5%) 2. n = 4 (2.0%) Serious TEAEs at 12 weeks 1. n = 1 (0.5%) 2. n = 1 (0.5%) Headache 1. n = 14 (9%) 2. n = 5 (2.5%)		**Risk of Bias (low/high/unclear)**: Selection Bias: see OASIS 1 Performance Bias: see OASIS 1 Detection Bias: see OASIS 1 Attrition Bias: see OASIS 1 Reporting Bias: see OASIS 1 Other Bias: see OASIS 1 **Applicability**: Patient: see OASIS 1 Intervention: see OASIS 1 Comparator: see OASIS 1 Outcomes: see OASIS 1 Setting: 77 sites in the United States, Canada, Czechia, Germany, Italy, Norway, Poland, Portugal, Slovakia, and Switzerland

		Never: 57% Former: 21% Current: 21% Placebo: Never: 68% Former: 17% Current: 16% <u>Key Inclusion Criteria</u>: see OASIS 1 <u>Key Exclusion Criteria</u>: see OASIS 1		LSM change in severity of moderate to severe hot flashes from baseline to week 4. 1. -0.75 2. -0.53 Difference: -0.22 95% CI -0.34 to -0.09; P=0.0003 LSM change in severity of moderate to severe hot flashes from baseline to week 12. 1. -0.91 2. -0.62 Difference: -0.29 95% CI -0.44 to -0.14; P<0.001 <u>Secondary Endpoints</u>: LSM change from baseline to week 12 in sleep disturbance as measured by the PROMIS SD SF 8b total t score. 1. -10.6 2. -5.5 Difference: -4.3 95% CI -5.8 to -2.9; P<0.001 LSM change from baseline to week 12 in menopause quality of life as assessed by the MENQOL total score. 1. -1.34 2. -0.97 Difference: -0.3 95% CI -0.5 to -0.1; P=0.0059	NA NA NA NA	<u>Fatigue</u> 1. n = 11 (5.5%) 2. n= 3 (1.5%) <u>Arthralgia</u> 1. n = 5 (2.5%) 2. n= 2 (1%) 95% CI and p-values NR		
Abbreviations: ARR = absolute risk reduction; DB = double-blind; CI = confidence interval; ITT = intention to treat; LSM = least square mean; MC = multi-center; MENQOL = Menopause-Specific Quality of Life; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PC = placebo controlled; PO = by mouth; PP = per protocol; PROMIS SD SF 8b = Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form; QDay = once daily; RCT = randomized controlled trial; TEAEs = Treatment-emergent adverse events; VMS = vasomotor symptoms; y = years.								

References:

1. LYNKUET (elinzanetant) Oral Capsules Prescribing Information. Whippany, NJ; Bayer HealthCare Pharmaceuticals, Inc. 10/2025.
2. Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. *JAMA*. 2024;332(16):1343-1354. doi:10.1001/jama.2024.14618
3. Cardoso F, Parke S, Brennan DJ, et al. Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer. Randomized Controlled Trial Clinical Trial, Phase III
Multicenter Study. *New England Journal of Medicine*. Aug 21 2025;393(8):753-763. doi:https://dx.doi.org/10.1056/NEJMoa2415566
4. Gartlehner G, Patel SV, Viswanathan M, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. *Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Women: An Evidence Review for the US Preventive Services Task Force*. Agency for Healthcare Research and Quality (US); 2017.
5. Crandall CJ, Mehta JM, Manson JE. Management of Menopausal Symptoms: A Review. *Jama*. Feb 7 2023;329(5):405-420. doi:10.1001/jama.2022.24140
6. Gold EB, Colvin A, Avis N, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health*. Jul 2006;96(7):1226-35. doi:10.2105/ajph.2005.066936
7. Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. *Health Qual Life Outcomes*. Aug 5 2005;3:47. doi:10.1186/1477-7525-3-47
8. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. Nov 2015;100(11):3975-4011. doi:10.1210/jc.2015-2236
9. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause*. Jun 1 2023;30(6):573-590.
10. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. Jul 1 2022;29(7):767-794.
11. DePree B. Fezolinetant: A Potential Treatment for Moderate to Severe Vasomotor Symptoms of Menopause. *touchREV Endocrinol*. Nov 2023;19(2):69-72. doi:10.17925/ee.2023.19.2.13
12. Food and Drug Administration Drug Safety Communication. September 12, 2024. FDA adds warning about rare occurence of serious liver injury with use of Veozah (fezolinetant) for hot flashes due to menopause. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-warning-about-rare-occurrence-serious-liver-injury-use-veozah-fezolinetant-hot-flashes-due Accessed 12/4/24.
13. Schultz NM, Morga A, Siddiqui E, Rhoten SE. Psychometric evaluation of the PROMIS SD-SF-8b instrument in individuals experiencing vasomotor symptoms due to menopause. *Health Qual Life Outcomes*. Nov 21 2023;21(1):126. doi:10.1186/s12955-023-02206-x
14. English M, Stoykova B, Slota C, et al. Qualitative study: burden of menopause-associated vasomotor symptoms (VMS) and validation of PROMIS Sleep Disturbance and Sleep-Related Impairment measures for assessment of VMS impact on sleep. *J Patient Rep Outcomes*. Apr 26 2021;5(1):37. doi:10.1186/s41687-021-00289-y
15. Hilditch JR, Lewis J, Peter A, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas*. 1996;24(3):161-175. doi:10.1016/S0378-5122(96)82006-8
16. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol*. May 2003;56(5):395-407. doi:10.1016/s0895-4356(03)00044-1
17. Center for Drug Evaluation and Research. Application Number: 219469Orig1s000. Risk Assessment and Risk Mitigation Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2025/219469Orig1s000RiskR.pdf Accessed 12/10/2025.
18. Micromedex (electronic version). IBM Watson Health, Greenwood Village, Colorado, USA. Available at http://www.micromedexsolutions.com. Accessed 12/12/2025.

19. Panay N, Joffe H, Maki PM, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: A Phase 3 Randomized Clinical Trial. *JAMA Intern Med*. Nov 1 2025;185(11):1319-1327. doi:10.1001/jamainternmed.2025.4421

Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LYNKUET® (elinzanetant) capsules, for oral use
Initial U.S. Approval: 2025

INDICATIONS AND USAGE

LYNKUET is a neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist indicated for the treatment of moderate to severe vasomotor symptoms due to menopause. (1)

DOSAGE AND ADMINISTRATION

The recommended dosage is 120 mg (two 60 mg capsules) orally once daily at bedtime with or without food. (2.2)

Swallow capsules whole. Do not cut, crush, or chew capsules. (2.2)

See full prescribing information for LYNKUET dosage modification due to drug interactions. (2.3)

DOSAGE FORMS AND STRENGTHS

Capsules: 60 mg (**3**)

CONTRAINDICATIONS

- Pregnancy. (4)

WARNINGS AND PRECAUTIONS

- CNS Depressant Effect and Daytime Impairment: Advise patients about the potential for somnolence and other nervous system effects. Advise patients who experience these effects to refrain from driving or engaging in hazardous occupations or activities until the effects have resolved (5.1)
- Hepatic Transaminase Elevations: Perform bloodwork prior to initiation of LYNKUET to evaluate for hepatic function and injury. Do not start therapy if serum transaminase concentration is equal to or exceeds two times the upper limit of normal (ULN). Perform follow-up evaluations of hepatic transaminase concentration 3 months after initiation. Do not start therapy if serum transaminase concentration is equal to or exceeds two times the ULN or if the total bilirubin is equal to or exceeds two times the ULN. Advise patients to discontinue LYNKUET immediately in case of signs or symptoms suggesting liver injury. (5.2)
- Risk of pregnancy loss: May cause pregnancy loss or stillbirth when administered during pregnancy. Exclude pregnancy in females of reproductive potential prior to initiating LYNKUET. Discontinue if pregnancy is confirmed (5.3)
- Risk of seizures in patients with a history of seizures (5.4)

ADVERSE REACTIONS

The most frequently reported (≥5%) adverse reactions were headache, fatigue, dizziness and somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors and grapefruit (juice): Avoid concomitant use with LYNKUET. (7.1)
- Moderate CYP3A4 Inhibitors: Reduce LYNKUET dosage to 60 mg once daily. (2.2, 7.1)
- Strong and Moderate CYP3A4 Inducers: Avoid concomitant use with LYNKUET. (7.1)

USE IN SPECIFIC POPULATIONS

- End Stage Renal Disease with or without hemodialysis: Not recommended. (8.6)
- Moderate to Severe Hepatic Impairment: Not recommended. (8.7)

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

Revised: 10/2025

Appendix 2. Elinzanetant Pharmacology and Pharmacokinetic Properties.[1]

Parameter	
Mechanism of Action	Neurokinin 1 and Neurokinin 3 receptor antagonist. Neurokinins are part of the neuronal activity which modulates thermoregulation associated with hot flashes.
Oral Bioavailability	52% following oral administration
Distribution and Protein Binding	Volume of distribution after intravenous administration: 137 liters. Plasma protein binding: 99.7%
Elimination	90% of dose is recovered in feces (50% unchanged) and less than 1% is recovered in urine.
Half-Life	45 hours
Metabolism	Metabolized by CYP3A4 hepatic enzymes to yield 3 active metabolites.

Appendix 3: Proposed Prior Authorization Criteria

Neurokinin Receptor Antagonists

Goal(s):
To ensure appropriate and safe use of neurokinin receptor antagonists in specified patient populations.

Length of Authorization:
- 6 to 12 months

Requires PA:
- Fezolinetant and elinzanetant

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.

Approval Criteria		
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 Document baseline frequency and severity of vasomotor symptoms_____	**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
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 request for fezolinetant?	**Yes:** Go to # 7	**No:** Go to #10
7. 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 #8

Approval Criteria		
8. Have baseline renal function tests been obtained?	**Yes:** Go to #9 and document baseline labs_____	**No:** Pass to RPh. Deny; medical appropriateness.
9. Is the estimated glomerular filtration rate less than 30 mL/min?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #14
10. Is the request for elinzanetant?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the patient taking a strong CYP3A4 inhibitor, strong CYP3A4 inducer, or moderate CYP3A4 inducer?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. Is the patient taking a moderate CYP3A4 Inhibitor?	**Yes:** Go to #13	**No:** Go to #14
13. Has the dose of elinzanetant been reduced to 60 mg once a day?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness
14. Have baseline liver function tests (AST, ALT, Alk Phos, and total bilirubin) been obtained?	**Yes:** Go to #15 Document baseline labs_____	**No:** Pass to RPh. Deny; medical appropriateness.
15. Do liver function tests indicate presence of hepatic injury (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 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 or 3 months after starting elinzanetant?	**Yes:** Go to #3 and document LFT results_____	**No:** Pass to RPh. Deny; medical appropriateness.
3. Do LFTs indicate hepatic injury (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: 4/26 (DM); 2/25; 6/24
Implementation: 6/1/26; 3/10/25; 7/1/24