# Elinzanetant (LYNKUET)
# National Drug Mini-Monograph
## September 2026
## VHA Pharmacy Services and National Formulary Committee

*The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.*

**Abbreviations**: AC, active-controlled; ALT=alanine aminotransaminase; AST=aspartate aminotransferase; CID=clinically important difference; CNS=central nervous system; CO, crossover; DB, double-blind; DILI=drug induced liver injury; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; LSM=Least Squares Means; MAIC=matching adjusted indirect comparison; MC, multicenter; MN, multinational; NMA=network meta-analysis; PC, placebo-controlled; RCT, randomized clinical trial; ULN=upper limit of normal

**VMS severity definitions:** mild = feeling of heat without sweating; moderate = feeling of heat with sweating but continue activity; severe = feeling of heat with sweating, causing cessation of activity

| SUMMARY OF PRESCRIBING INFORMATION[1,2] | |
|---|---|
| **Description / MOA** | Elinzanetant is a neurokinin 1 (NK1) and neurokinin 3 (NK3) receptor antagonist. Inhibition of substance P and neurokinin B through antagonism of NK1 and NK3 receptor signaling on kisspeptin/neurokinin B/ dynorphin (KNDy) neurons can modulate neuronal activity in thermoregulation associated with hot flashes. |
| **Indication Under Review** | Treatment of moderate to severe vasomotor symptoms (VMS) due to menopause |
| **Dosage Regimen** | 120 mg (two 60 mg capsules) orally once daily at bedtime; reduced dose with certain drug interactions |
| **Dosage Forms Under Review** | 60 mg oral capsules |
| **Boxed Warnings** | None |
| **Contraindications** | Pregnancy |
| **Other Warnings** | ▪ **CNS depressant effect and daytime impairment:** CNS depressant effects including somnolence, fatigue, vertigo, dizziness, and presyncope were reported more frequently with elinzanetant vs. placebo (11.9% vs. 3.5% in OASIS trials). Advise patients on the potential for somnolence and CNS effects and to refrain from driving or hazardous activities until effects have resolved.<br>▪ **Hepatic transaminase elevations:** Perform baseline hepatic bloodwork (AST, ALT, alkaline phosphatase, total and direct bilirubin) prior to initiation of elinzanetant. Do not initiate if transaminases or total bilirubin are 2 or more times ULN. Recheck hepatic bloodwork at 3 months after initiation and counsel patients on signs and symptoms of liver injury. Discontinue if transaminases are elevated greater than 5x ULN or if transaminases are elevated greater than 3x ULN and total bilirubin exceeds 2x ULN.<br>▪ **Risk of pregnancy loss:** Animal studies suggest that elinzanetant can cause pregnancy loss or stillbirth. Exclude pregnancy in patients of reproductive potential. Use effective contraception (if at risk of pregnancy) for the duration of treatment and for two weeks after stopping.<br>▪ **Risk of seizures (in patients with seizure history):** One patient on elinzanetant with a remote history of seizures experienced seizures during the clinical trials. Postmarketing cases of seizures have been reported. Convulsions were observed in animal studies. Elinzanetant should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold. |
| **Common AEs** | Headache, fatigue, dizziness, somnolence, abdominal pain |
| **Drug Interactions** | ▪ **CYP3A4 inhibitors** increase elinzanetant exposure and potential for adverse effects. **Avoid** concomitant use of elinzanetant with strong CYP3A4 inhibitors and **reduce dose** of elinzanetant with moderate CYP3A4 inhibitors.<br>▪ **CYP3A4 inducers** reduce elinzanetant exposure and possibly effectiveness. **Avoid** concomitant use of elinzanetant with strong CYP3A4 inducers.<br>▪ **CYP3A4 substrates** – Elinzanetant is a weak CYP3A4 inhibitor and increases exposure of CYP3A4 substrates. **Avoid** concomitant use unless otherwise recommended for the CYP3A4 substrate. |
| **Pregnancy** | Contraindicated; may cause pregnancy loss or stillbirth. Exclude pregnancy prior to use. |
| **Lactation** | No data |
| **Renal Impairment** | No dosage adjustment needed for eGFR ≥15 mL/min; no data on eGFR <15 mL/min or dialysis |
| **Hepatic Impairment** | No adjustment for mild (Child-Pugh A). Not recommended for moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment |

## EFFICACY CONSIDERATIONS

**Overview**

FDA approval of elinzanetant was primarily based on two double-blind, placebo-controlled, industry-sponsored phase 3 trials (OASIS 1 and OASIS 2) in naturally or surgically postmenopausal women with at least 50 moderate-to-severe hot flashes per week during screening. Supporting evidence was provided by the 52-week OASIS 3 trial, which evaluated a broader population seeking treatment for VMS with no minimum frequency requirement. In the OASIS-4 trial, elinzanetant was evaluated in women (aged 18 to 70) with breast cancer (or at high risk) and experiencing endocrine therapy-induced VMS.

**Trial**

**OASIS 1 and 2[3]**

**Design**

Similar design - MC, MN, DB, PC, RCT, **26-week duration**, industry sponsored

**Primary Endpoint**

Mean change in frequency and severity of moderate to severe VMS from baseline to weeks 4 and 12

**Population**

Naturally or surgically postmenopausal women (40-65 years) with ≥50 moderate to severe VMS/week. Patients were excluded if they had hepatic lab abnormalities or cancer. Hormone therapy was not permitted.

**Interventions**

Patients were randomized 1:1 to receive elinzanetant 120 mg or placebo orally once daily for 12 weeks. Then, all patients received elinzanetant 120 mg orally daily for 14 weeks. All patients were then followed for 4 weeks post treatment.

**Baseline**

$N_R$ OASIS-1 = 399; $N_R$ OASIS-2 = 397; Mean age 55 yrs, Mean VMS frequency 13-16 daily; Mean VMS severity 2.5; Mean duration amenorrhea 5 yrs; Pts with hysterectomy 35-42%; White 76-86%; Black 13-19%; Hispanic 7-12%; 85% and 87% completed OASIS-1 and 2, respectively.

**Efficacy Results**

| OASIS-1 and OASIS-2 Primary Endpoint week 12 | OASIS-1 | | OASIS-2 | |
|---|---|---|---|---|
| | ELINZ N=199 | PBO N=197 | ELINZ N=200 | PBO N=200 |
| **Frequency of moderate-severe VMS per day** | | | | |
| Baseline (#) | 13.4 | 14.3 | 14.7 | 16.2 |
| Δ from baseline to 12 wks | -8.7 | -5.4 | -9.7 | -6.5 |
| Treatment difference vs. PBO | -3.2 | | -3.2 | |
| **Severity of moderate-severe VMS*** | | | | |
| Baseline (mean) | 2.6 | 2.5 | 2.5 | 2.5 |
| Δ from baseline at 12 wks | -0.9 | -0.5 | -0.9 | -0.6 |
| Treatment difference vs. PBO | -0.4 | | -0.3 | |

P <0.05 for all comparisons at weeks 4 (not shown) and 12. Changes expressed LSM; *Severity scale: mild, moderate, severe were given 1, 2, or 3 pts respectively. Onset of improvement with elinzanetant was seen at one week and continued throughout the 26-week treatment period.

Key secondary endpoints (12 wks): Elinzanetant was associated with patient reported improvements from baseline in sleep disturbances (PROMIS SD SF 8b total T scores) compared to placebo (-5.6 and -4.3 in OASIS-1 and OASIS-2, respectively; minimal CID: -3 to -5) and small improvements in the MENQOL total score vs. placebo. Seventy-one to 75% of patients in OASIS-1 and 2 achieved at least a 50% reduction in VMS (vs. 42% and 48% in placebo groups).

**Conclusions/ Limitations**

Elinzanetant was more effective than placebo in reducing moderate to severe VMS and in improving sleep disturbances. Limitations include use of placebo control instead of active treatment and short duration of randomized treatment.

**Trial**

**OASIS 3[4]**

**Design**

MC, MN, DB, PC, RCT, **52-week duration,** industry sponsored

**Primary Endpoint**

Mean change in frequency of daily moderate to severe VMS from baseline to week 12

**Population**

Naturally or surgically postmenopausal women (40-65 years) seeking treatment for moderate to severe VMS (no minimum requirements). Patients were excluded if they had hepatic lab abnormalities or cancer. Hormone therapy was not permitted.

**Interventions**

Patients were randomized 1:1 to receive elinzanetant 120 mg or placebo orally once daily for 52 weeks.

**Baseline**

$N_R$ = 628; Mean age 55 yrs, Mean moderate-to-severe VMS frequency 6.7 daily; Mean duration amenorrhea 7 yrs; Pts with hysterectomy 29%; White 78%; Black 15%; Hispanic 11%

**Efficacy Results**

| OASIS-3 Primary Endpoint Week 12 | ELINZ N=313 | PBO N=315 |
|---|---|---|
| **Frequency of moderate-severe VMS per day** | | |
| Baseline (#) | 6.7 | 6.8 |
| Δ from baseline to 12 wks | -5.4 | -3.5 |
| Treatment difference vs. PBO | -1.6 | |

p <0.05; Changes expressed as LSM

Key secondary and exploratory endpoints were not powered to detect between group differences.

**Conclusions/ Limitations**

Elinzanetant was more effective than placebo in reducing moderate to severe VMS. Limitations include placebo instead of active control and lack of power to detect between group differences for secondary and exploratory endpoints.

| | |
|---|---|
| **Trial** | **OASIS 4**[5] |
| **Design** | MC, MN, DB, PC, RCT, **52-week duration,** industry sponsored |
| **Primary Endpoint** | Mean change in frequency of daily moderate to severe VMS from baseline to week 4 and to week 12 |
| **Population** | Women aged 18 to 70 years who were receiving endocrine therapy (tamoxifen or aromatase inhibitor with or without GnRH analogues) for **hormone receptor (HR) positive breast cancer or its prevention** (in patients at high risk for breast cancer). Patients had to have at least 35 moderate-to-severe VMS per week associated with endocrine therapy. |
| **Interventions** | Patients were randomized 2:1 to elinzanetant 120 mg or placebo orally once daily for 12 weeks, followed by all patients receiving elinzanetant 120 mg once daily for 40 weeks. Patients were followed for an additional 4 weeks after treatment concluded. |
| **Baseline** | $N_R$ = 474; Mean age 51 yrs, Mean moderate-to-severe VMS frequency 11 daily; Tamoxifen 56%; Aromatase inhibitors 44%;Mean duration endocrine tx 19 mos; White 88%; Black 1%; Hispanic or Latino 3%; all but one patient using endocrine therapy for breast cancer (not prevention); 94% completed 12 wks; 83% completed 52 wks |
| **Efficacy Results** | |

| **OASIS-4 Primary Endpoint Weeks 4 and 12** | **ELINZ N=316** | **PBO N=158** |
|---|---|---|
| **Frequency of moderate-severe VMS per day** | | |
| Baseline (#) | 11.4 | 11.5 |
| Δ from baseline to 4 wks | -6.5 | -3.0 |
| Treatment difference vs. PBO | -3.5 | |
| Δ from baseline to 12 wks | -7.8 | -4.2 |
| Treatment difference vs. PBO | -3.4 | |

p <0.05; Changes expressed as LSM

- Key secondary endpoints: Elinzanetant was associated with patient reported improvements from baseline in sleep disturbances (PROMIS SD SF 8b total T scores) compared to placebo at week 12 (-6.1 points; minimal clinically important difference: -3 to -5) and in the mean MEQOL total score (-0.7 points; minimal clinically important difference -0.9).

| | |
|---|---|
| **Conclusions/ Limitations** | Elinzanetant was more effective than placebo in reducing frequency of moderate to severe VMS. Limitations include placebo instead of active control, short duration of randomized treatment, and lack of generalizability to the population receiving endocrine therapy for high risk of breast cancer. |

## SAFETY CONSIDERATIONS[1,2]

**Safety Results**

Evaluation of safety for FDA approval was primarily based on a total of 1,420 women from OASIS-1, OASIS-2, and OASIS-3 trials. Duration of exposure ranged from 12 to 52 weeks. There were no deaths reported.

| **Adverse Event (%)** | **OASIS-1 and OASIS-2 (pooled)** | | **OASIS-3** | |
|---|---|---|---|---|
| | ELINZ (N=400) | PBO (N=393) | ELINZ (N=313) | PBO (N=314) |
| DC due to AE | 7.5 | 4.3 | 12.5 | 4.1 |
| Serious AEs | 1.2 | 0.8 | 4.2 | 1.9 |

- **Serious adverse events:** SAEs were varied with no clear pattern or safety signals (see Table).
- **Discontinuation due to adverse events (elinzanetant vs. placebo):** Common reasons included abdominal pain, fatigue, depression, and headache (see Table).
- **Common adverse events (≥5%):** headache, fatigue, dizziness, somnolence

**Selected safety data from FDA review**

- **Hepatic safety** was evaluated as a special AE of interest due to 1) nonclinical data supporting hepatotoxicity; 2) hepatic transaminases elevations (ALT and/or AST) observed in Phase 1 and 2 studies; and 3) known hepatoxicity risk with an NK3 inhibitor fezolinetant. There were no cases meeting Hy's law criteria in phase 2b or 3 studies. There was an increased frequency of transaminase elevations (ALT or AST) of greater than 3x ULN in clinical trials; however, no excess of elevations greater than 5x ULN were seen. There were two cases of DILI attributed to elinzanetant.
- **Endometrial safety** was evaluated in OASIS-1, 2, and 3 and was within the expected threshold for safety.
- **CNS effects:** Excess CNS effects were observed with elinzanetant, including AEs leading to discontinuation such as fatigue, somnolence, dizziness, and vertigo. Onset is within 10 days of initiation. A dedicated safety study to evaluate driving performance showed that driving ability was impaired in some subjects taking single or repeat doses of elinzanetant.

## OTHER CONSIDERATIONS

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|---|---|
| **Studies of Potential Interest** | Across three 2026 indirect analyses, fezolinetant and elinzanetant appear to be similarly effective and safe for reducing VMS frequency and severity, with elinzanetant showing an advantage in sleep improvement.[6,7,8] Elinzanetant was superior to other nonhormonal options including paroxetine and desvenlafaxine. Limitations include industry sponsorship, indirectness, and one analysis with a pending Expression of Concern.[8] |

| NONHORMONAL THERAPEUTIC ALTERNATIVES FOR VMS | | | | |
|---|---|---|---|---|
| **Drug** | **MOA** | **Formulary status** | **Effectiveness†** | **Other Considerations** |
| **FDA Approved for moderate-to-severe VMS** | | | | |
| **Elinzanetant (LYNKUET) (120 mg daily, bedtime)** | NK1, NK3 antagonist | TBD | -3.2 VMS per day vs. PBO (12 wk) | CNS depressant, LFT monitoring, seizure risk, CYP3A4 drug interactions |
| **Fezolinetant (VEOZAH) (45 mg daily)** | NK3 antagonist | NF with CFU | -2.5 VMS per day vs. PBO (12 wk) | Hepatotoxicity and LFT monitoring, CYP1A2 inhibitor interaction |
| **Paroxetine mesylate (7.5 mg daily)** | SSRI | NF | -1.5 per day vs. PBO | Cannot use with tamoxifen |
| **Off-label with evidence supporting effectiveness** | | | | |
| **Citalopram (10-20 mg daily)** | SSRI | F | 27 – 61% composite improvements in VMS severity and frequency | None |
| **Escitalopram (10-20 mg daily)** | SSRI | F | | None |
| **Paroxetine (10-25 mg daily)** | SSRI | F | | Cannot use with tamoxifen |
| **Desvenlafaxine (100-150 mg daily)** | SNRI | F | | None |
| **Venlafaxine (37.5-150 mg daily)** | SNRI | F | | None |
| **Gabapentin (900-2400 mg daily)** | Gaba-pentinoid | F | -2.8 per day vs. PBO | May benefit patients with VMS affecting sleep |
| **Oxybutynin (2.5 or 5 mg IR twice daily) (up to 15 mg ER daily)** | Anti-cholinergic | F | -5 VMS per day vs. PBO | Use limited by anticholinergic AEs, cognitive decline |

†Studies differed in design, population, and outcomes; therefore, the ability to draw comparisons of effectiveness between agents is limited.

| POTENTIAL PLACE IN THERAPY[1,2] | |
|---|---|
| **Summary of Evidence and Place in Therapy** | 1. Efficacy of elinzanetant was demonstrated in OASIS-1 and 2, where elinzanetant reduced the frequency of moderate to severe VMS by about 3.2 per day vs. placebo, meeting a clinical threshold for a reduction of at least 2 VMS per day.[2] Severity of VMS and sleep disturbances were also improved. In the OASIS-4 trial, a dedicated study of breast cancer patients experiencing endocrine therapy–related VMS, elinzanetant similarly reduced VMS frequency compared with placebo. In OASIS-1, 2, and 4, baseline moderate-to-severe VMS ranged from 11 to 16 per day.<br>2. Safety data for elinzanetant is available for a duration of up to 52 weeks. Elinzanetant was associated with CNS-related adverse effects (e.g., somnolence, fatigue, dizziness). Although no clear hepatotoxicity signal was identified in phase 3 trials, elevated transaminases and cases of drug induced liver injury were reported, resulting in the need for baseline and 3-month hepatic lab work. Elinzanetant is contraindicated in pregnancy and may increase the risk of seizures in patients with a seizure history.<br>3. Up to 80% of women experience VMS during the menopausal transition.[9] In the U.S., the prevalence of moderate to severe VMS is 34%.[10] The median total duration of VMS has been reported to be 7.4 years, with a median of 4.5 years following the final menstrual period. Compared to other races and ethnicities, Black women reported a longer VMS total median duration of 10 years.[11] Though not life threatening, VMS can greatly impact quality of life and interfere with normal activities in some women. Based on diagnosis data over the past 4 quarters, estimates of Veterans with a menopausal state or bilateral oophorectomy diagnosis is approximately 35,300.<br>4. Menopausal hormone therapy (MHT) is the most effective treatment for moderate to severe VMS and confers additional benefits (genitourinary symptoms, sleep, and bone health). MHT remains first line therapy for women who are younger than 60 years old and within 10 years of their final menstrual period if there are no contraindications (e.g., breast cancer or estrogen sensitive cancer, venous thromboembolic event, stroke, or coronary heart disease).<br>5. For patients with contraindications or who choose to avoid MHT, several nonhormonal pharmacologic options are available for VMS treatment. Elinzanetant, fezolinetant, and paroxetine mesylate (BRISDELLE) are FDA approved for moderate-to-severe VMS, while multiple SSRIs, SNRIs, and gabapentin are used off-label and supported by evidence.<br>6. Elinzanetant, a dual NK1/NK3 receptor antagonist, is the second neurokinin-pathway treatment available in the U.S. Fezolinetant, an NK1 receptor antagonist, was approved in 2023. Though there are limitations in the analyses, indirect comparisons suggest similar efficacy between agents for VMS, with elinzanetant showing a possible advantage on sleep outcomes. No direct comparison randomized trials are available. Another potential advantage of elinzanetant includes dedicated evidence of benefit in endocrine therapy-associated VMS in a breast cancer population. Hepatic monitoring is required for both agents. In an industry-sponsored indirect comparative analysis, elinzanetant was found to be superior to paroxetine and desvenlafaxine and similar to fezolinetant for reducing VMS frequency.<br>7. The cost of elinzanetant is similar to fezolinetant and significantly higher than other nonhormonal options. An ICER (Institute for Clinical and Economic Review) is not available for elinzanetant but was conducted with fezolinetant in 2022.[12] ICER concluded that the net health benefits of fezolinetant 45 mg vs. no treatment for VMS was promising but inconclusive, given the modest reduction in VMS in RCTs and uncertain long-term benefit and safety. Based on an economic evaluation, they concluded that for fezolinetant to be considered cost-effective relative to accepted benchmarks in 2022, it would have to be priced at about $2,000 annually. In 2026, National Institute for Health and Care Excellence (NICE) recommended that fezolinetant can be used as an option to treat moderate-to-severe VMS when MHT is unsuitable, concluding that cost-effectiveness is within an acceptable range for National Health Service Resources.[13] Of note, the cost of fezolinetant in the NICE report is far lower than U.S. costs.<br>8. SSRIs, SNRIs, and gabapentin remain reasonable nonhormonal options for VMS treatment given their modest efficacy, well-known adverse effect profiles, utility in comorbid conditions (e.g., mood disorders, neuropathic pain), lack of lab monitoring, and low cost. It appears that elinzanetant is similar to fezolinetant in efficacy for VMS based on indirect comparisons with limitations. Elinzanetant may have an advantage in sleep disturbances. There are some differences in safety and adverse effect profiles. It is unclear whether there are clinically meaningful advantages in efficacy of elinzanetant (or fezolinetant) over SSRIs, SNRIs, and gabapentin given the limitations with the available analyses. |

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