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Review Article

Elinzanetant: Dual Neurokinin-1/Neurokinin-3 Receptor Antagonism for Menopausal Vasomotor Symptoms

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ABSTRACT

Background: Menopausal vasomotor symptoms (VMS), principally hot flashes and night sweats, are common manifestations of the menopause transition and can persist for years. They are associated with sleep disruption, impaired daily functioning, and reduced quality of life. Menopausal hormone therapy (MHT) is highly effective for appropriately selected patients, but it is not suitable for everyone, including many women with hormone-sensitive malignancies or specific thromboembolic and cardiovascular histories. The identification of hypothalamic kisspeptin/neurokinin B/dynorphin (KNDy) circuitry as a key regulator of thermoregulatory stability has enabled mechanism-based nonhormonal drug development. Objective: To review the neuroendocrine rationale, pharmacology, clinical evidence, safety, regulatory status, and clinical positioning of elinzanetant, an orally active dual neurokinin-1 (NK1) and neurokinin-3 (NK3) receptor antagonist. Methods: This narrative review draws on pivotal randomized trials, dose-finding research, long-term clinical data, regulatory product information, menopause cohort studies, and reviews of KNDy physiology. It distinguishes directly observed clinical outcomes from proposed mechanistic explanations and identifies areas where detailed evidence remains limited. Results: In the two pivotal Phase 3 OASIS-1 and OASIS-2 trials, elinzanetant 120 mg once daily at bedtime reduced moderate-to-severe VMS frequency versus placebo at Weeks 4 and 12. Placebo-adjusted least-squares mean differences in daily VMS frequency were −3.3 and −3.0 episodes at Week 4, and −3.2 episodes in each trial at Week 12; all comparisons were statistically significant. Reductions were evident by Week 1. At Week 12, at least 50% VMS-frequency reduction occurred in 71.4% and 74.7% of elinzanetant recipients in OASIS-1 and OASIS-2, respectively, compared with 42.0% and 48.3% on placebo. Sleep-disturbance and menopause-related quality-of-life scores also improved.

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OASIS-3 provided 52-week placebo-controlled data in a broader population and found sustained efficacy signals and no hepatotoxicity signal, although the study was not designed to establish every secondary or exploratory endpoint through formal hypothesis testing. OASIS-4 reported efficacy for VMS associated with breast-cancer endocrine therapy, a population with substantial unmet need. The US label identifies headache, fatigue, dizziness, and somnolence among common adverse reactions and requires baseline and three-month hepatic testing. Elinzanetant was approved in the United States in 2025 and received European Union marketing authorization in November 2025 for moderate-to-severe VMS due to menopause. Conclusions: Elinzanetant adds a mechanistically targeted nonhormonal option for moderate-to-severe menopausal VMS. Its dual receptor pharmacology and observed improvements in sleep-related patient-reported outcomes are clinically relevant, but mechanistic hypotheses should not be mistaken for demonstrated normalization of human sleep architecture. Prescribing decisions should follow the current local product information, especially hepatic testing, drug-interaction, CNS-impairment, seizure-history, pregnancy, and organ-impairment precautions.

INTRODUCTION

2. Introduction and Clinical Background

Menopause is a retrospective clinical diagnosis in people with spontaneous menstrual cycles after 12 consecutive months of amenorrhea without another physiological or pathological explanation. The menopause transition, often called perimenopause in clinical communication, is the interval of changing menstrual-cycle regularity leading up to the final menstrual period and the first year thereafter.

Reproductive aging is driven chiefly by depletion of ovarian follicles and altered ovarian steroid production. Estradiol concentrations fluctuate substantially during the transition before becoming persistently low after menopause; gonadotropins, particularly follicle-stimulating hormone, generally rise as ovarian negative feedback diminishes. Surgical removal of both ovaries can produce an abrupt fall in ovarian hormones and a different symptom trajectory from natural menopause [17-21].

VMS include episodic heat sensations, flushing, sweating, and sometimes subsequent chills or shivering. The subjective experience ranges from mild warmth to intense episodes that interrupt work, social activities, concentration, and sleep. Night sweats may prompt repeated awakenings, while daytime events can be embarrassing or disruptive. VMS should not be regarded simply as a peripheral skin response: the prevailing model places altered central thermoregulation at the center of symptom generation, with autonomic effectors translating a small thermoregulatory perturbation into cutaneous vasodilation and sweating [7,21,32].

Prevalence estimates vary with population, definition, sampling, and stage of reproductive aging. Many studies report that a majority of women experience VMS, and estimates approaching 80% are often cited for some populations. However, prevalence is not a single universal constant. Symptoms differ by ethnicity, body composition, smoking, socioeconomic context, psychological factors, and cultural interpretation or reporting. The Study of Women's Health Across the Nation (SWAN) is especially important because it followed women longitudinally through the transition rather than relying solely on cross-sectional surveys. SWAN analyses identified variation in symptom frequency and duration across racial and ethnic groups, with African American women on average reporting longer-lasting VMS than several comparison groups [11,12,21].

Duration is a central clinical issue. In the SWAN analysis reported by Avis and colleagues, the median total duration of frequent VMS was approximately 7.4 years, and symptoms beginning during perimenopause could persist for several years after the final menstrual period. Duration varies substantially between individuals, and some women report symptoms for a decade or longer [12]. Thus, short-term management alone may be inadequate for patients with persistent symptoms, while long-term therapy requires evidence on sustained benefit and safety.

MHT, usually systemic estrogen with a progestogen for patients with an intact uterus, remains among the most effective therapies for bothersome VMS. Its benefit-risk profile depends on age, time since menopause, formulation, dose, route, uterine status, comorbidities, and individual preferences. The Women's Health Initiative (WHI) trials changed public and clinical

perceptions because specific regimens—particularly oral conjugated equine estrogen plus medroxyprogesterone acetate in the studied population—were associated with increased risks of outcomes including venous thromboembolism, stroke, and breast cancer; coronary outcomes also require careful interpretation in relation to regimen and baseline risk [24,25]. These findings should not be generalized into a claim that every hormone regimen carries identical risks, nor do they mean all women should avoid MHT.

Systemic MHT is generally avoided in women with a history of hormone-sensitive breast cancer and may be inappropriate in people with prior thromboembolism, stroke, coronary disease, unexplained vaginal bleeding, or active liver disease, depending on the clinical context and local guidance. Women taking tamoxifen or aromatase inhibitors may experience substantial treatment-associated VMS while needing to avoid systemic estrogen. In addition, some patients prefer nonhormonal treatment after informed discussion. The unmet need is therefore not that hormones are universally unsafe, but that a sizeable subgroup needs effective alternatives [13,14,23,26].

The burden extends beyond symptom scores. Sleep fragmentation can affect fatigue, mood, and perceived cognitive efficiency. Women with severe symptoms report reduced work productivity, presenteeism, absenteeism, and changes in career plans. Healthcare use can rise when symptoms are mistaken for other disorders or when repeated consultations are required to manage persistent symptoms. Economic estimates vary by country and methodology, so global cost claims should be interpreted cautiously; nonetheless, the combination of symptom prevalence, duration, and functional impairment makes VMS an important public-health and workplace issue [21,22].

The emergence of neurokinin receptor antagonists represents a shift from replacing a deficient hormone to modifying neural signaling involved in symptom generation. Elinzanetant is a dual NK1/NK3 antagonist. Its evidence base includes randomized trials in postmenopausal women and a trial in women experiencing VMS during endocrine treatment for breast cancer. The distinction between a nonhormonal mechanism and suitability for every patient is important: elinzanetant has its own contraindications, drug interactions, hepatic monitoring requirements, and CNS precautions.

3. Central Pathophysiology of Menopausal VMS and KNDy Circuitry

3.1 Thermoregulatory organization: preoptic area and arcuate nucleus

Core temperature is maintained by integrated neural networks that compare thermal information with defended physiological ranges and coordinate heat production and heat loss. The preoptic area (POA) of the anterior hypothalamus is a major integrative region for thermoregulatory control. It receives

peripheral and central thermal signals and influences downstream autonomic and behavioral responses. The arcuate nucleus (ARC), in the mediobasal hypothalamus, contains neuroendocrine populations that integrate reproductive, metabolic, and temperature-related information. KNDy neurons in the ARC are now understood to be relevant to both reproductive hormone feedback and thermoregulatory function [7,27,34].

The thermoneutral zone is the range of core temperatures over which the body can maintain temperature without initiating major heat-loss or heat-conservation responses. The leading model of VMS proposes that this range becomes abnormally narrow during estrogen withdrawal. In such a state, a small fluctuation in core temperature can cross the threshold for heat dissipation, producing an abrupt flush and sweating episode. The model is supported by physiological observations and animal work, but exact circuit-level details in humans remain an active area of investigation.

3.2 Kisspeptin, neurokinin B, and dynorphin: KNDy signaling

KNDy neurons co-express kisspeptin, neurokinin B (NKB), and dynorphin. Kisspeptin is a potent regulator of gonadotropin-releasing hormone (GnRH) neurons and therefore reproductive endocrine signaling. NKB acts primarily through the neurokinin-3 receptor (NK3R), while dynorphin acts through kappa-opioid receptors and contributes inhibitory feedback within the network. The coordinated activity of these neuropeptides helps generate rhythmic signaling relevant to reproductive function. KNDy neurons also project to

or interact with pathways influencing thermoregulation, making them a plausible bridge between ovarian hormone withdrawal and hot flashes [7,27,34].

Estradiol acts through estrogen receptors, including estrogen receptor alpha (ERα), to regulate hypothalamic gene expression and neuronal activity. In the presence of ovarian feedback, KNDy neurons are subject to inhibitory regulation. Following the decline in estradiol around menopause, experimental models show increased KNDy neuronal size and expression of neuropeptide-related markers. These findings have been important in establishing the biological plausibility of the KNDy hypothesis.

However, statements about specific transcriptional changes or cell hypertrophy should be anchored to the species and experimental conditions studied rather than assumed to be directly measured in living menopausal human hypothalami [7,27,34].

3.3 Estrogen withdrawal and thermoregulatory instability

When ovarian estrogen feedback diminishes, increased KNDy activity and NKB signaling can influence thermoregulatory circuits. NK3R signaling is therefore a pharmacologically tractable target. In the hypothalamic model, heightened excitatory signaling makes thermoregulatory responses easier to trigger. Once a threshold is crossed, autonomic output promotes cutaneous vasodilation and sweating. These responses increase heat loss and may be followed by a subjective chill as body temperature falls or the autonomic response resolves. Palpitations or a sensation of a racing heart can accompany episodes, though symptom patterns vary.

This framework explains why VMS may be episodic despite chronically low estrogen: the trigger is not a continuously elevated body temperature, but instability in the neural thresholds governing thermoregulatory responses. It also helps explain why nonhormonal NK3 antagonists can reduce VMS without restoring estrogen concentrations. Nevertheless, VMS are heterogeneous, and sleep, mood, medication effects, medical comorbidities, and environmental factors may modify symptom experience.

3.4 Rationale for dual NK1/NK3 antagonism

Elinzanetant antagonizes both NK3 and NK1 receptors. NK3 antagonism is directly linked to interruption of NKB-mediated signaling implicated in thermoregulatory instability. NK1 receptors are activated by substance P, a neuropeptide involved in nociception, stress-related signaling, autonomic responses, and central arousal networks. Dual blockade therefore provides a plausible rationale for addressing VMS and associated sleep disturbance within one molecule. The US product information describes inhibition of substance P and NKB signaling through NK1 and NK3 receptor antagonism on KNDy-related pathways as a mechanism that may modulate neuronal activity involved in hot flashes [5,6].

It is tempting to state that NK1 antagonism specifically normalizes sleep architecture or that it independently shortens wake after sleep onset (WASO). Such claims require direct mechanistic or polysomnographic evidence. The pivotal OASIS studies demonstrate improvements in patient-reported sleep disturbance using the PROMIS Sleep Disturbance Short Form, but those findings do not by themselves prove a particular receptor-specific effect or preservation of each sleep stage. Accordingly, sleep benefits should be presented as clinical observations, while the proposed NK1-mediated explanation remains mechanistic interpretation.

Dual receptor blockade may offer broader symptom coverage than selective NK3 antagonism, but cross-trial comparisons cannot establish superiority. Differences in trial populations, baseline symptom burden, outcome definitions, follow-up, and statistical design complicate indirect comparisons with fezolinetant or other therapies. Head-to-head randomized trials would be needed to establish comparative efficacy, sleep benefits, tolerability, or cost-effectiveness.

4. Chemical Profile and Drug Summary

Elinzanetant, previously designated NT-814, is a synthetic, orally active, nonhormonal small molecule developed to antagonize human NK1 and NK3 receptors. The commercial name in the United States and European Union is Lynkuet. The approved US indication is treatment of moderate-to-severe VMS due to menopause. The European Commission granted

marketing authorization in November 2025 for moderate-to-severe menopausal VMS. The US FDA approval also occurred in 2025 [1,5,9].

Parameter	Evidence-based description
Generic name	Elinzanetant (formerly NT-814)
Brand name	Lynkuet
Drug class	Dual neurokinin-1 (NK1) and neurokinin-3 (NK3) receptor antagonist
Mechanism	Antagonism of substance P/NK1 and NKB/NK3 signaling relevant to thermoregulatory neural circuits
US approved indication	Moderate-to-severe vasomotor symptoms due to menopause

Dose	**120 mg orally once daily at bedtime; two 60-mg capsules in the US label**
Administration	With or without food; capsules swallowed whole
Important monitoring	Liver tests before treatment and at 3 months under US prescribing information
Key interaction issue	CYP3A4 inhibitors/inducers; see current label for avoidance or dose modification
Regulatory status	US approval in 2025; EU marketing authorization issued 17 November 2025
Special-population evidence	OASIS-4 studied VMS associated with endocrine therapy for breast cancer; do not infer a separate approved indication unless local label states it

Illustrative product presentations

Figure 1: ***Illustrative product presentations of Lynkuet (elinzanetant) 60 mg capsules.***



The drug is not a hormone and does not aim to replace estradiol. Its development reflects a target-based approach in which a hypothalamic neuropeptide circuit is modulated to reduce symptoms. The regulatory label—not an older review or promotional summary—should be the controlling source for dosing, contraindications, warnings, and required laboratory testing.

5. Detailed Pharmacology and Pharmacokinetics

5.1 Receptor pharmacology and selectivity

Elinzanetant binds human NK1 and NK3 receptors with greater affinity than the NK2 receptor. The US prescribing information reports pKi ranges of 8.7–10.2 for NK1, 8.0–8.8 for NK3, and approximately 6.0 for NK2 [5]. A pKi value is the negative base-10 logarithm of an inhibition constant expressed in molar units; higher pKi indicates stronger affinity. These values should not be casually converted into a single universal Ki because the reported ranges reflect assay context and receptor preparations. Receptor affinity also does not by itself establish clinical potency, receptor occupancy in a particular brain region, or the relative contribution of each target to efficacy.

NK1 receptors preferentially respond to substance P, whereas NK3 receptors are the principal receptor for NKB. Elinzanetant is described as an antagonist at both targets. Its activity at NK2 is materially weaker, supporting a degree of pharmacological selectivity. In vitro selectivity does not imply absence of all off-target or class-related effects, and the clinical safety profile must be evaluated independently through controlled studies and postmarketing surveillance.

5.2 Absorption, distribution, and elimination

According to the US label, absolute oral bioavailability is approximately 52%. At steady state, median time to maximum plasma concentration is about 1 hour, with a reported range of 1 to 2.5 hours. A high-fat meal did not produce clinically meaningful changes in pharmacokinetics, consistent with administration with or without food. The mean steady-state volume of distribution after intravenous dosing is approximately 137 L, and plasma protein binding is 99.7%. These values are preferable to secondary summaries that report a Tmax

of 1.5–3 hours without identifying the conditions under which it was measured [5].

The reported elimination half-life in women with VMS is approximately 45 hours, rather than the 14–22 hours stated in some draft summaries. Steady-state concentrations are reached over roughly 5–14 days, and accumulation at the recommended dose is less than twofold. Following a radiolabeled oral dose in healthy subjects, approximately 90% of administered radioactivity was recovered in feces, around half as unchanged drug, while less than 1% was recovered in urine. These findings indicate that fecal elimination predominates and that renal excretion of unchanged parent drug is small [5].

5.3 Metabolism and drug interactions

Elinzanetant is primarily metabolized by CYP3A4 to form three major active metabolites (identified in the label as M18/21, M27, and M30/34). The metabolites have similar potency at human NK1 and NK3 receptors to the parent compound. This is an important distinction from a model in which only the parent molecule contributes to pharmacological activity. The label reports that elinzanetant and its metabolites inhibit CYP3A4; elinzanetant is also a weak CYP3A4 inhibitor in vivo, increasing exposure to the sensitive CYP3A4 substrate midazolam [5].

Strong CYP3A4 inhibitors and grapefruit juice should be avoided. For moderate CYP3A4 inhibitors, the US label reduces the elinzanetant dose to 60 mg once daily. Strong and moderate CYP3A4 inducers should be avoided because they may lower exposure and compromise efficacy. Carbamazepine substantially reduced elinzanetant exposure in interaction studies. The label also advises avoiding coadministration with CYP3A4 substrates for which even modest concentration increases could lead to serious adverse reactions unless the substrate's own prescribing information provides an appropriate approach [5].

Medication reconciliation should include prescription drugs, over-the-counter products, and herbal supplements. A general warning to 'avoid CYP3A4 interactions' is not enough: the correct action depends on inhibitor or inducer strength, the co-medication, and the current label. Patients should not start or stop interacting medication without review by a qualified clinician or pharmacist.

5.4 Special populations and pharmacodynamic considerations

The US label does not recommend elinzanetant in end-stage renal disease or moderate-to-severe hepatic impairment. Exposure can be altered by renal impairment, although population analyses described in the label did not find clinically meaningful differences for mild or moderate renal impairment in trial participants. The details should be interpreted with care because single-dose pharmacokinetic findings and population analyses are not interchangeable. No clinically relevant QTc prolongation was observed after single oral doses up to five times the recommended maximum dose; however, the QTc effect with strong CYP3A4 inhibitors was not sufficiently characterized [5].

The label includes warnings for CNS depressant effects and daytime impairment, hepatic transaminase elevations, pregnancy-related risk, and seizures in people with a seizure history. Therefore, bedtime

administration is not evidence that next-day impairment cannot occur. Patients who experience somnolence, dizziness, or other nervous-system effects should avoid driving or hazardous activities until symptoms resolve.

6. Clinical Trial Program and Evidence Base

6.1 Phase 2 dose-finding: SWITCH-1

SWITCH-1 was a randomized, double-blind, placebo-controlled Phase 2 dose-finding study of elinzanetant in postmenopausal women with moderate-to-severe VMS. The study evaluated multiple doses, including 40, 80, 120, and 160 mg daily, and assessed changes in VMS frequency and severity as well as sleep and quality-of-life outcomes. The trial established a dose-response basis for selecting 120 mg for Phase 3 development. It is important to avoid overstating the results as a uniform dose-dependent effect at every dose and every endpoint: the published report found that 120 mg and 160 mg reduced VMS frequency versus placebo from Week 1, while statistically significant placebo-adjusted reductions were demonstrated at selected primary time points [2,6].

For 120 mg, the least-squares mean placebo-adjusted reduction in VMS frequency was −3.93 episodes per day at Week 4 (standard error 1.02; P<0.001) and −2.95 at Week 12 (standard error 1.15; P=0.01). For 160 mg, the placebo-adjusted reduction at Week 4 was −2.63 episodes per day (standard error 1.03; P=0.01). These results support efficacy but do not imply that 160 mg is more effective than 120 mg. The selection of a dose for Phase 3 incorporates tolerability, dose-response, and the totality of efficacy and safety data, not simply the largest nominal dose.

The study also assessed patient-reported sleep and quality of life. Improvements in these outcomes were encouraging and provided a rationale for more detailed assessment in Phase 3. However, small Phase 2 samples are not sufficient to establish rare safety risks, long-term durability, or a definitive receptor-specific sleep mechanism.

6.2 Pivotal Phase 3 trials: OASIS-1 and OASIS-2

OASIS-1 (NCT05042362) and OASIS-2 (NCT05099159) were multinational, randomized, double-blind, placebo-controlled trials in postmenopausal women aged 40–65 years with moderate-to-severe VMS. Participants received elinzanetant 120 mg once daily or placebo for 12 weeks; those initially assigned to placebo then switched to elinzanetant for a further 14 weeks, yielding 26 weeks of total study exposure. The two trials enrolled 796 participants in total. Baseline VMS burden was substantial: mean frequency was 13.4 versus 14.3 events per 24 hours in the OASIS-1 active and placebo groups and 14.7 versus 16.2 in OASIS-2 [1,3].

The primary endpoints evaluated changes in frequency and severity of moderate-to-severe VMS at Weeks 4 and 12. In OASIS-1, the placebo-adjusted least-squares mean difference in daily VMS frequency was

−3.3 episodes at Week 4 (95% CI −4.5 to −2.1; P<0.001) and −3.2 at Week 12 (95% CI −4.8 to −1.6;

P<0.001). In OASIS-2, corresponding differences were −3.0 at Week 4 (95% CI −4.4 to −1.7; P<0.001) and −3.2 at Week 12 (95% CI −4.6 to −1.9; P<0.001). These are placebo-adjusted differences, not the total within-group decline; the distinction matters because placebo responses were substantial [1].

Endpoint	OASIS-1: elinzanetant vs placebo	OASIS-2: elinzanetant vs placebo
VMS frequency, Week 4, LS mean difference	**−3.3/day (95% CI −4.5 to −2.1), P<0.001**	**−3.0/day (95% CI −4.4 to −1.7), P<0.001**
VMS frequency, Week 12, LS mean difference	−3.2/day (95% CI −4.8 to −1.6), P<0.001	−3.2/day (95% CI −4.6 to −1.9), P<0.001
VMS severity, Week 4, LS mean difference	−0.3 (95% CI −0.4 to −0.2), P<0.001	−0.2 (95% CI −0.3 to −0.1), P<0.001
VMS severity, Week 12, LS mean difference	−0.4 (95% CI −0.5 to −0.3), P<0.001	−0.3 (95% CI −0.4 to −0.1), P<0.001
≥50% reduction in frequency, Week 12	71.4% vs 42.0%	74.7% vs 48.3%

The onset of action was evident by Week 1. Placebo-adjusted reductions in frequency at Week 1 were

−2.5 episodes per day in OASIS-1 (95% CI −3.4 to −1.6; P<0.001) and −1.7 in OASIS-2 (95% CI −2.7 to

−0.6; P=0.001). By Week 4, 62.8% and 62.2% of participants receiving elinzanetant in OASIS-1 and OASIS-2 achieved at least a 50% reduction in VMS frequency, compared with 29.2% and 32.3% on placebo. At Week 12, responder rates rose to 71.4% and 74.7%, compared with 42.0% and 48.3% on placebo [1].

Sleep disturbance was assessed with the PROMIS Sleep Disturbance Short Form 8b. At Week 12, the placebo-adjusted difference in total T score was −5.6 in OASIS-1 (95% CI −7.2 to −4.0; P<0.001) and

−4.3 in OASIS-2 (95% CI −5.8 to −2.9; P<0.001). Menopause-related quality of life, measured with MENQOL, also improved: the placebo-adjusted total-score difference was −0.4 in OASIS-1 (95% CI

−0.6 to −0.2; P<0.001) and −0.3 in OASIS-2 (95% CI −0.5 to −0.1; P=0.0059) [1]. These patient-reported outcomes support benefits beyond hot-flash counts,

although they do not establish that all sleep complaints or cognitive symptoms will improve in every patient.

Adverse events in the 12-week placebo-controlled period were generally mild or moderate. In OASIS-1, any treatment-emergent adverse event occurred in 51.3% of participants on elinzanetant and 48.5% on placebo; in OASIS-2, the corresponding proportions were 44.3% and 38.2%. Headache and fatigue were among the most frequently reported events. Discontinuations due to adverse events occurred in 8.5% versus 6.7% in OASIS-1 and 6.5% versus 2.0% in OASIS-2. These figures are more informative than a generalized statement that discontinuation was below 5%, which is not consistent with both pivotal-trial arms [1].

6.3 OASIS-3: 52-week efficacy and safety

OASIS-3 (NCT05030584) was a 52-week randomized, double-blind, placebo-controlled Phase 3 trial in 628 postmenopausal women aged 40–65 years. Unlike OASIS-1 and OASIS-2, it did not require a minimum weekly number of VMS events, broadening the clinical population studied. Participants were

randomized to elinzanetant 120 mg daily or placebo for the full 52 weeks. Baseline symptom frequency was lower than in the pivotal registration trials, at approximately 6.7–6.8 moderate-to-severe VMS events per day [8].

At Week 12, mean change in daily moderate-to-severe VMS frequency was −5.4 in the elinzanetant group and −3.5 in the placebo group. The least-squares mean difference was −1.6 episodes per day (95% CI

−2.0 to −1.1; P<0.001). Secondary and exploratory outcomes over later weeks were primarily descriptive and the study was not powered to test every long-term endpoint as a formal superiority hypothesis. The data showed numerical advantages in VMS frequency and severity over 50 weeks and sleep disturbance and quality-of-life measures over 52 weeks [8].

Treatment-related adverse events were more common with elinzanetant than placebo (30.4% vs 14.6%); somnolence, fatigue, and headache were frequent treatment-related events. The study did not identify a hepatotoxicity signal, endometrial hyperplasia or malignant endometrial neoplasm signal, or meaningful changes in bone density or bone-turnover markers. These observations are reassuring but do not eliminate the need for the liver monitoring now required in the US label, nor do they prove absence of very rare or delayed adverse effects [8].

6.4 OASIS-4: VMS during breast-cancer endocrine therapy

OASIS-4 (NCT05587296) addressed a clinically important group: women with moderate-to-severe VMS associated with adjuvant endocrine therapy for breast cancer. Tamoxifen and aromatase inhibitors can cause or aggravate menopausal symptoms, while systemic estrogen is generally avoided in patients with hormone-sensitive breast cancer. This creates a need for non-hormonal therapies that reduce symptoms without compromising oncologic treatment. OASIS-4 was a randomized, placebo-controlled trial and its results were published in the New England Journal of Medicine in 2025 [10,16].

The study found that elinzanetant led to a significantly lower frequency of VMS associated with endocrine therapy than placebo. This supports consideration of elinzanetant as a potential option in a population with high unmet need, but the wording of clinical recommendations must remain aligned with local labeling, oncology guidance, and each patient's treatment plan. A trial's inclusion of women receiving tamoxifen or aromatase inhibitors is not by itself proof that all drug interactions, recurrence outcomes, or long-term oncologic endpoints have been definitively resolved.

The evidence should be interpreted in the context of the trial's primary endpoint and follow-up. Symptom efficacy is not equivalent to a demonstrated effect on breast-cancer recurrence or survival. Oncologists and menopause clinicians should coordinate care, especially when patients are receiving multiple medications or have hepatic comorbidity.

6.5 Sleep and quality-of-life outcomes: what is demonstrated?

Across OASIS-1 and OASIS-2, PROMIS Sleep Disturbance Short Form 8b scores improved significantly relative to placebo by Week 12. MENQOL total scores also improved, with the largest changes occurring in the VMS domain [1]. These validated patient-reported measures capture perceived sleep disturbance and

menopause-related quality of life and provide clinically meaningful complementary outcomes to symptom diaries.

The supplied draft asserted that polysomnography and actigraphy substudies confirmed reduced WASO and nocturnal awakenings without disruption of REM or N3 sleep. Those specific claims were not

confirmed in the primary trial reports reviewed for this synthesis and should not be presented as established facts without a traceable substudy publication. Similarly, a statistically significant PROMIS improvement should not be described as direct evidence that NK1 antagonism independently normalizes sleep-stage architecture. Further mechanistic and objective sleep research would help clarify the relative roles of VMS reduction, substance P signaling, and other contributors to nocturnal sleep disruption.

7. Population Consistency and Subgroup Analyses

Subgroup analyses are useful for assessing whether an average treatment effect is plausibly consistent across clinically relevant groups, but they are rarely powered to demonstrate efficacy independently in every subgroup. The OASIS program enrolled women across age and racial/ethnic categories and included naturally and surgically postmenopausal participants. OASIS-3 broadened the symptom-frequency range, while OASIS-1 and OASIS-2 enrolled women with at least 50 moderate-to-severe hot flashes per week. These differences matter when comparing apparent effect sizes between studies [1,8].

7.1 Age and time since menopause

The pivotal trials enrolled women aged 40–65 years, with mean age approximately 54.6 years. The results therefore apply most directly to a midlife population within this age range. They should not automatically be extrapolated to older adults, adolescents, or people with premature ovarian insufficiency without additional evidence. Clinical factors such as time since final menstrual period, concurrent disease, and medication burden may influence treatment choice even when they do not materially alter the pharmacological mechanism.

7.2 BMI and metabolic context

BMI is associated with VMS reporting and may affect symptom patterns, but it should not be assumed that each BMI category has a precisely identical treatment effect unless the published interaction analysis supports that conclusion. The provided draft claimed uniform efficacy for BMI <25, 25–30, and ≥30 kg/m², but no detailed effect estimates or interaction statistics were supplied. A rigorous review should state that subgroup data are supportive only to the extent documented in trial reports and avoid inventing separate efficacy percentages.

7.3 Natural versus surgical menopause

Surgical menopause can result in abrupt ovarian hormone withdrawal, whereas natural menopause typically involves a transition with fluctuating ovarian function. OASIS-3 included naturally and surgically postmenopausal women, improving the breadth of evidence. Nonetheless, subgroup inclusion does not prove that the magnitude of benefit is identical in both groups. For patients with surgery-related VMS, the choice of treatment should also reflect the indication for surgery, cancer history, age, bone health, and whether hormone therapy is appropriate.

7.4 Race, ethnicity, and generalizability

The OASIS-3 population included White, Black/African American, and Hispanic/Latina participants, although White participants made up the majority. Representation of Asian and other populations was more limited in the trials summarized here. No clinically significant pharmacokinetic differences based on race were identified in the US label [5]. This is not equivalent to proof that symptom response, adherence,

access, or patient-reported outcomes are identical across every ethnic group. Diverse real-world data and transparent reporting of subgroup estimates remain important.

Overall, available data support a broad role for elinzanetant in the studied population, but the paper should not imply fully powered equivalence across all BMI, age, ethnicity, or menopause-type categories. Such claims require published subgroup estimates, confidence intervals, and formal interaction tests.

8. Safety, Tolerability, and Hepatic Evaluation

8.1 Common adverse reactions and CNS effects

The US prescribing information identifies headache, fatigue, dizziness, and somnolence as the most frequently reported adverse reactions, each occurring in at least 5% of treated participants in the relevant pooled clinical-trial safety data [5]. The exact rates differ across trials and treatment periods; therefore, rates should be tied to the relevant study rather than combined into an unsupported range. Most events in the pivotal studies were mild or moderate, but adverse events leading to discontinuation were not negligible in every arm [1].

Bedtime dosing is intended to align administration with the nocturnal burden of symptoms, but somnolence and other CNS effects can extend into the following day. Patients should be counselled about driving, operating machinery, falls risk, and hazardous activities if they experience dizziness or sedation. Concurrent CNS depressants may increase impairment, and the full medication list should be reviewed.

8.2 Hepatic monitoring: a material prescribing requirement

The earlier draft stated that routine liver-function monitoring was not required. That statement conflicts with the US FDA-approved prescribing information. The US label directs clinicians to obtain bloodwork before initiation to evaluate hepatic function and injury, not to start treatment if serum transaminases are at least two times the upper limit of normal, and to repeat transaminases three months after initiation. The label also contains advice about stopping treatment and assessing symptoms suggestive of liver injury [5]. The current local product information should be checked because regulatory requirements can differ and may be updated.

OASIS-3 reported no hepatotoxicity signal under the trial's monitoring and adjudication procedures [8]. That is reassuring evidence, but it does not negate the regulatory monitoring requirement. A distinction must be maintained between 'no hepatotoxicity signal observed in the clinical trial' and 'no monitoring is needed in clinical practice.' The latter is not supported by the current US label.

The neurokinin-antagonist class has a history of liver-safety scrutiny, including concerns with some NK3-targeting compounds. This background helps explain why hepatic outcomes were followed closely during elinzanetant development. A rigorous assessment considers laboratory trends, timing, competing causes, clinical symptoms, bilirubin, and independent adjudication rather than relying solely on a statement that no Hy's Law cases occurred. The trial data summarized here are reassuring, but claims such as 'zero Hy's Law cases across every study' should be made only if directly documented in the specific source.

8.3 Contraindications, warnings, and interactions

Pregnancy is a contraindication under the US label, which warns of possible pregnancy loss or stillbirth based on animal reproduction studies. Pregnancy should be excluded in females of reproductive potential before treatment, and treatment should be discontinued if pregnancy is confirmed. The label also warns

about seizures in patients with a history of seizures. These points are important even though elinzanetant is intended for menopausal symptoms [5].

Strong CYP3A4 inhibitors and grapefruit juice should be avoided; moderate inhibitors require a reduction to 60 mg once daily; and strong or moderate CYP3A4 inducers should be avoided. Moderate-to-severe hepatic impairment and end-stage renal disease are populations in which use is not recommended under the US label. Clinicians should review the complete current label rather than extrapolating from the pharmacokinetic section alone [5].

8.4 Comparison with other nonhormonal options

SSRIs and SNRIs, gabapentin, and other nonhormonal approaches may be appropriate for selected patients, depending on comorbidities, symptom profile, prior response, and adverse-effect tolerance. SSRIs/SNRIs can cause gastrointestinal effects, sexual dysfunction, sleep changes, or discontinuation symptoms; gabapentin may cause dizziness and sedation. Elinzanetant has a different mechanism, but its somnolence, fatigue, dizziness, interaction burden, and liver testing requirements must also be considered. It is not scientifically appropriate to claim it is categorically

better tolerated than SSRIs, SNRIs, or gabapentinoids without direct comparative trials.

For women with a history of breast cancer, selection among nonhormonal therapies should consider the oncology regimen and potential interactions. The OASIS-4 evidence is particularly relevant, but it should be integrated with oncology advice and current local authorization. Shared decision-making should discuss expected benefits, uncertainty, monitoring, costs, and alternatives.

9. Clinical Guidelines, Prescribing Considerations, and Future Horizons

The standard US regimen is 120 mg orally once daily at bedtime, taken with or without food; the capsules should be swallowed whole. The US label specifies two 60-mg capsules for the 120-mg dose. If a bedtime dose is missed, the label instructs the patient to take the next dose as scheduled the following day rather than taking two doses on the same day. Dose modifications for CYP3A4 interactions are important and should be checked before prescribing [5].

Before treatment, clinicians should assess VMS burden, sleep and functional impact, menopausal status, pregnancy potential where relevant, seizure history, liver health, renal status, concurrent medications, and patient preferences. Baseline hepatic bloodwork and follow-up transaminases at three months are required by the US label. Patients should be advised to report symptoms potentially consistent with liver injury, including unusual fatigue, anorexia, nausea, dark urine, or jaundice, and to seek clinical assessment promptly.

Elinzanetant is an option for patients who prefer nonhormonal therapy or for whom systemic MHT is unsuitable. However, a history of breast cancer, cardiovascular disease, or thromboembolism should not be reduced to a simple algorithm that automatically makes one specific drug the correct choice. Treatment selection should consider all relevant risks and the patient's values. OASIS-4 adds evidence for VMS during endocrine therapy for breast cancer, while the exact approved indication and any restrictions must be verified in the jurisdiction where treatment is considered.

Future work should examine treatment persistence, real-world effectiveness, comparative effectiveness versus other neurokinin antagonists and established nonhormonal therapies, long-term safety beyond one year, and cost-effectiveness. Surgical menopause and chemotherapy-induced ovarian insufficiency are

plausible areas for study, but results from natural menopause populations cannot be assumed to transfer without dedicated evidence. Research into mood instability, cognition, and objective sleep measures should distinguish symptoms secondary to VMS from independent neuropsychiatric or sleep disorders.

Mechanistic research should also clarify whether dual NK1/NK3 antagonism produces clinically meaningful effects beyond those expected from NK3 blockade alone. Direct head-to-head trials, mediation analyses, pharmacodynamic biomarkers, and polysomnography studies could help determine whether changes in sleep are primarily downstream of fewer nocturnal hot flashes or reflect additional central effects. Until such data are available, the most defensible statement is that elinzanetant improves patient-reported sleep disturbance in randomized trials, not that it has been proven to preserve every stage of sleep architecture.

10. Conclusion and Declarations

Elinzanetant is a dual NK1/NK3 receptor antagonist developed for moderate-to-severe menopausal VMS. Its mechanism is grounded in the role of KNDy neuronal networks in linking ovarian hormone feedback with hypothalamic thermoregulatory control. The pivotal OASIS-1 and OASIS-2 trials demonstrated statistically significant reductions in VMS frequency and severity, with benefits apparent by Week 1 and improvements in patient-reported sleep disturbance and menopause-related quality of life. OASIS-3 extended the evidence to 52 weeks in a broader population, while OASIS-4 addressed VMS associated with breast-cancer endocrine therapy.

The clinical evidence supports elinzanetant as an important nonhormonal option, not as a universally superior replacement for MHT or other therapies. Interpretation must account for placebo response, differences between trial populations, the distinction between primary and descriptive long-term endpoints,

and the limited evidence for some subgroup-specific or mechanistic claims. Safety considerations include somnolence, fatigue, dizziness, headache, drug interactions, pregnancy risk, seizure-history warnings, and hepatic testing.

Regulatory product information is decisive for clinical use. In the United States, liver testing is required before treatment and at three months, strong CYP3A4 inhibitors and grapefruit juice should be avoided, moderate CYP3A4 inhibitors require dose reduction, and moderate-to-severe hepatic impairment and end-stage renal disease are not recommended populations. Future comparative and real-world studies will refine elinzanetant's place in individualized menopause care.

Declarations

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