

Elinzanetant

A non-hormonal, orally bioavailable dual NK1/NK3 receptor antagonist developed through GlaxoSmithKline, NeRRe Therapeutics, KaNDy Therapeutics, and Bayer for the treatment of moderate-to-severe vasomotor symptoms associated with menopause, distinguished from selective NK3 antagonists by concurrent blockade of substance P signaling and consequent additive benefits on sleep, mood, and thermoregulatory dysregulation.

DOCUMENT	KDC-MN-1627
ISSUED	2026-05-21
REVISION	1.0
AUTHOR	Kodiac biolabs Research
COMPOUND CLASS	Dual neurokinin-1 (NK1) and neurokinin-3 (NK3) receptor antagonist for non-hormonal treatment of menopausal vasomotor symptoms

ABSTRACT

Elinzanetant (Lynkuet; BAY3427080; formerly NT-814 and GSK1144814) is a potent and selective dual antagonist of the neurokinin-1 (NK1) and neurokinin-3 (NK3) receptors, developed for the non-hormonal treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause and with endocrine therapy for hormone receptor-positive breast cancer. The compound received its first regulatory approval in the United Kingdom in July 2025, followed by approvals in Australia, Canada, Switzerland, and the United States, where it was approved by the Food and Drug Administration on October 24, 2025, under the trade name Lynkuet at a recommended dose of 120 mg orally once daily at bedtime. Elinzanetant is the first and only approved dual NK1/NK3 receptor antagonist, mechanistically distinct from fezolinetant (Veoza[®]), which acts solely on the NK3 receptor. The dual mechanism targets kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the hypothalamic arcuate nucleus, where neurokinin B (NKB) acting through NK3 receptors initiates thermoregulatory dysregulation responsible for hot flashes, and substance P (SP) acting through NK1 receptors amplifies KNDy neuronal activity and contributes to sleep disruption, mood disturbance, and peripheral vasodilation. By antagonizing both receptor subtypes, elinzanetant addresses the composite symptom burden of menopause rather than isolated hot flash frequency alone. The compound exhibits high affinity for human NK1 receptors (pK_i 8.7 to 10.2) and NK3 receptors (pK_i 8.0 to 8.8), with greater than 300-fold selectivity for NK1 and greater than 100-fold selectivity for NK3 over off-target receptors. Pharmacokinetics are characterized by rapid oral absorption

(median T_{max} approximately 1 hour), absolute oral bioavailability of 52 percent, extensive plasma protein binding (99.7 percent), a large volume of distribution (137 L), and a long elimination half-life of approximately 45 hours that supports once-daily dosing. Metabolism is predominantly CYP3A4-mediated, producing three active metabolites with comparable NK1/NK3 potency at approximately 39 percent of parent plasma exposure. Excretion is predominantly fecal (90 percent as metabolites). The clinical evidence base comprises the OASIS Phase 3 program: OASIS 1 and OASIS 2 (12-week placebo-controlled studies in approximately 400 postmenopausal women each), OASIS 3 (52-week long-term study in 628 women), and OASIS 4 (12-week study in women receiving breast cancer endocrine therapy). All trials met primary endpoints, demonstrating statistically significant and clinically meaningful reductions in VMS frequency and severity at weeks 4 and 12, with onset of effect as early as week 1. Secondary endpoints showed significant improvements in sleep disturbances, menopause-related quality of life, and mood. Long-term efficacy was maintained through 52 weeks in OASIS 3 with no signal of hepatotoxicity, endometrial hyperplasia, or endometrial malignancy. The most common adverse events are headache (7.8 percent) and fatigue (5 percent). Elinzanetant is contraindicated in pregnancy, in severe hepatic impairment, and with concomitant strong CYP3A4 inhibitors. This monograph reviews the chemistry, synthesis, and stereochemistry of elinzanetant; the dual-receptor pharmacology in molecular and neurophysiological detail; the comprehensive human pharmacokinetic record; the clinical evidence base across the OASIS program and the dose-finding SWITCH-1 study; sourcing and quality verification considerations; reconstitution and handling; stack-interaction considerations for research applications; the adverse-event and safety signal profile;

and a comparative assessment of five alternative compounds for vasomotor symptom management against elinzanetant on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Elinzanetant.

Marketed name: Lynkuet (Bayer; United States, United Kingdom, Australia, Canada, Switzerland).

Development codes: BAY3427080 (Bayer), NT-814 (KaNDy Therapeutics/NeRRe Therapeutics), GSK1144814 (GlaxoSmithKline). The NT-814 code is the canonical identifier in the early clinical pharmacology literature, including the Phase 1 healthy volunteer studies and the SWITCH-1 dose-finding trial. The GSK1144814 designation appears in the earliest pharmacokinetic characterization studies pre-dating the divestiture from GlaxoSmithKline [1].

Chemical Abstracts Service registry number: 929046-33-3 (free base).

International Union of Pure and Applied Chemistry name: N-[6-[(7S,9aS)-7-(hydroxymethyl)-3,4,6,7,9,9a-hexahydro-1H-pyrazino[2,1-c][1,4]oxazin-8-yl]-4-(4-fluoro-2-methylphenyl)pyridin-3-yl]-2-[3,5-bis(trifluoromethyl)phenyl]-N,2-dimethylpropanamide.

PubChem Compound Identifier: CID 16063568.

DrugBank Identifier: DB18968.

1.2 Structural class and chemistry

Elinzanetant is a small-molecule heterocyclic compound containing a central pyridine ring linked to a hexahydropyrazino-oxazine bicyclic system bearing a hydroxymethyl substituent, a bis(trifluoromethyl)phenyl-substituted dimethylpropanamide moiety, and a fluoromethylphenyl group. The structural class places it within the neurokinin receptor antagonist family, a group of compounds that includes aprepitant (NK1 antagonist), fosaprepitant, netupitant, and fezolinetant (NK3 antagonist). Elinzanetant is distinguished from these agents by its dual NK1/NK3 binding profile within a single molecular entity [2, 3].

Molecular formula: C₃₃H₃₅F₇N₄O₃.

Molecular weight: 668.65 g/mol (free base).

Physical properties: White to yellowish powder. Practically insoluble in water at neutral pH; slightly soluble under acidic conditions. The compound is formulated as soft capsules containing 60 mg of elinzanetant for oral administration [4].

Stereochemistry: Elinzanetant contains two defined stereocenters at the 7- and 9a-positions of the hexahydropyrazino[2,1-c][1,4]oxazine ring system, with the (7S,9aS) absolute configuration. The stereochemical configuration is critical for receptor binding affinity and selectivity; the compound is supplied as the single defined stereoisomer in all clinical and research formulations.

1.3 Synthesis

The published synthesis of elinzanetant proceeds through construction of the hexahydropyrazino-oxazine bicyclic ring system with defined stereochemistry at the 7S,9aS positions, followed by coupling to the central pyridine scaffold, introduction of the 4-fluoro-2-methylphenyl substituent, and acylation with the bis(trifluoromethyl)phenyl-bearing propanamide side chain. The seven fluorine atoms (two trifluoromethyl groups and one aryl fluoride) confer metabolic stability and contribute to the lipophilicity that supports oral bioavailability and central nervous system penetration. Industrial synthesis routes are proprietary to Bayer and are not disclosed in full detail in the public literature. The compound is manufactured under Good Manufacturing Practice for the marketed pharmaceutical product and is available from research chemical suppliers at research-grade purity for investigational applications [5].

2. Abstract

Elinzanetant (Lynkuet; BAY3427080; NT-814) is the first approved dual neurokinin-1 and neurokinin-3 receptor antagonist, developed for the non-hormonal treatment of moderate-to-severe vasomotor symptoms (VMS) associated with menopause [2, 3]. The compound targets kisspeptin/neurokinin B/dynorphin (KNDy) neurons in the hypothalamic arcuate nucleus, a neuronal population that serves as the central thermoregulatory pacemaker and that becomes hyperactive in the estrogen-depleted state characteristic of menopause and of pharmacological ovarian suppression during breast cancer endocrine therapy [6, 7].

The pharmacological rationale for dual NK1/NK3 antagonism rests on the distinct but complementary roles of neurokinin B (NKB) and substance P (SP) in the KNDy neuronal circuit. NKB, acting through NK3 receptors, is the primary autocrine and paracrine signal that drives KNDy neuronal firing and the consequent thermoregulatory dysregulation experienced as hot flashes [8]. SP, acting through NK1 receptors, amplifies KNDy neuronal excitability and additionally contributes to sleep disruption, mood dysregulation, and peripheral vasodilation through projections to brainstem and cortical targets [9]. By antagonizing both receptor subtypes, elinzanetant addresses the composite menopausal symptom burden (hot flashes, night sweats, sleep disturbance, mood disturbance, impaired quality of life) rather than the isolated hot flash frequency endpoint targeted by selective NK3 antagonists such as fezolinetant [10].

The clinical evidence base is anchored by the OASIS Phase 3 program: four randomized, double-blind, placebo-controlled trials enrolling a combined population of approximately 2,000 women [11, 12, 13, 14]. All trials met their primary endpoints. In OASIS 1 and OASIS 2, elinzanetant 120 mg daily produced statistically significant and clinically meaningful reductions in VMS frequency and severity versus placebo at weeks 4 and 12, with onset of effect observed as early as week 1. In OASIS 3, efficacy was maintained through 52 weeks with a favorable long-term safety profile. In OASIS 4, elinzanetant produced comparable efficacy in women experiencing VMS secondary to breast cancer endocrine therapy, a population in whom hormonal therapy is contraindicated. The most common adverse events were headache (7.8 percent) and fatigue (5 percent), with no signal of hepatotoxicity, endometrial hyperplasia, or endometrial malignancy [13].

Elinzanetant received its first regulatory approval in the United Kingdom in July 2025, followed by approvals in Australia, Canada, Switzerland, and the United States (FDA approval October 24, 2025) [2]. The compound is marketed by Bayer under the trade name Lynkuet as 60 mg soft capsules, administered as two capsules (120 mg total) orally once daily at bedtime. This monograph reviews the complete pharmacology, pharmacokinetics, clinical evidence, safety profile, sourcing, handling, and comparative positioning of elinzanetant in the context of the broader neurokinin receptor antagonist class and alternative non-hormonal therapies for vasomotor symptoms.

3. Discovery and Development History

3.1 Origin

Elinzanetant was initially synthesized at GlaxoSmithKline as GSK1144814, a dual NK1/NK3 receptor antagonist identified through medicinal chemistry optimization within a program targeting neurokinin receptors for central nervous system and neuroendocrine indications. The compound was among several neurokinin receptor antagonist candidates characterized during the 2000s, a period of extensive pharmaceutical industry investment in tachykinin pharmacology following the clinical success of aprepitant (the first marketed NK1 antagonist, approved for chemotherapy-induced nausea and vomiting in 2003) [1, 15].

Early pharmacokinetic and central nervous system penetration studies of GSK1144814 were conducted in healthy volunteers, including a study in alcohol-intoxicated volunteers that characterized the compound's pharmacokinetic profile and established brain NK1 receptor occupancy using cranial imaging techniques [1].

3.2 Divestiture and spinout

In 2012, NeRRe Therapeutics Ltd was founded to develop neurokinin antagonist assets divested from GlaxoSmithKline. NeRRe acquired the rights to GSK1144814 (re-designated NT-814) and repositioned the compound toward menopausal vasomotor symptoms, a therapeutic application that had emerged from growing understanding of the role of KNDy neurons in thermoregulation [6, 7]. In 2017, KaNDy Therapeutics Ltd was spun out of NeRRe Therapeutics specifically to support the clinical development of elinzanetant for VMS, with the company name reflecting the KNDy neuron hypothesis that underpinned the therapeutic rationale [2].

3.3 Phase 1 and Phase 2 development

KaNDy Therapeutics conducted Phase 1 studies characterizing the pharmacokinetics, pharmacodynamics, and safety of elinzanetant in healthy premenopausal and postmenopausal women. A key Phase 1 finding was that elinzanetant dose-depen-

dently reduced serum estradiol and luteal-phase progesterone in healthy premenopausal women, consistent with modulation of the hypothalamic-pituitary-gonadal axis through KNDy neuron antagonism [16]. Cranial imaging studies demonstrated dose-dependent NK1 receptor occupancy in the human brain with an EC₅₀ of approximately 0.9 ng/mL [2].

The SWITCH-1 Phase 2b dose-finding study randomized postmenopausal women aged 40 to 65 years with moderate-to-severe VMS to multiple elinzanetant doses or placebo. The 120 mg once-daily dose produced the most favorable efficacy-tolerability balance, with VMS frequency reductions of 3.93 per day versus placebo at week 4 (p less than 0.001) and 2.95 per day versus placebo at week 12 (p equals 0.01) [17]. This dose was selected for Phase 3 development.

3.4 Acquisition by Bayer and Phase 3 development

In August 2020, Bayer AG acquired KaNDy Therapeutics, gaining full rights to elinzanetant. Bayer redesignated the compound BAY3427080 and initiated the OASIS Phase 3 program, comprising four pivotal trials: OASIS 1 and OASIS 2 (replicate 12-week efficacy studies in postmenopausal VMS), OASIS 3 (52-week long-term safety and efficacy study), and OASIS 4 (12-week efficacy study in breast cancer endocrine therapy-associated VMS) [11, 12, 13, 14].

3.5 Regulatory approval

The New Drug Application was submitted to the FDA in late 2024. The FDA extended the review period and subsequently approved elinzanetant on October 24, 2025, for the treatment of moderate-to-severe VMS due to menopause. The United Kingdom Medicines and Healthcare products Regulatory Agency granted the first global approval on July 10, 2025. The European Medicines Agency Committee for Medicinal Products for Human Use recommended approval in September 2025 for moderate-to-severe VMS in menopause and for VMS associated with breast cancer endocrine therapy [2].

4. Mechanism of Action

Elinzanetant is a dual-target ligand. Its principal molecular activities are competitive antagonism at the NK1 receptor (the primary receptor for substance P) and competitive antagonism at the NK3 receptor (the primary receptor for neurokinin B). These activities operate at functionally relevant concentrations achieved by the approved 120 mg oral dose and contribute differentially to the observed reductions in vasomotor symptoms, sleep disturbance, and mood dysregulation.

4.1 KNDy neuron physiology and menopausal thermoregulatory dysfunction

The kisspeptin/neurokinin B/dynorphin (KNDy) neuronal population in the hypothalamic arcuate nucleus is the central node governing reproductive neuroendocrine function and thermoregulation. KNDy neurons co-express three neuropeptides: kisspeptin (a potent activator of gonadotropin-releasing hormone neurons), neurokinin B (an autocrine/paracrine activator of KNDy neuronal firing through NK3 receptors), and dynorphin (an inhibitory opioid peptide that provides negative feedback on KNDy activity) [6, 7, 8].

In the premenopausal state, estrogen restrains KNDy neuronal activity through estrogen receptor alpha-mediated transcriptional suppression. In menopause, the loss of ovarian estrogen production removes this inhibitory restraint, resulting in KNDy neuronal hypertrophy, increased NKB and SP expression, and dysregulated high-frequency firing. The dysregulated KNDy output projects to the median preoptic nucleus and other thermoregulatory centers, narrowing the thermoneutral zone and triggering inappropriate heat-dissipation responses (cutaneous vasodilation, sweating) experienced as hot flashes and night sweats [6, 7, 18].

4.2 NK3 receptor antagonism

The NK3 receptor (neurokinin 3 receptor; TACR3 gene product) is a G protein-coupled receptor of the tachykinin receptor family, expressed on KNDy neurons themselves (mediating autocrine/paracrine NKB signaling), on neurons of the median

preoptic nucleus (mediating thermoregulatory output), and at lower density in other hypothalamic and limbic regions [8].

Elinzanetant binds human NK3 receptors with high affinity (pKi 8.0 to 8.8, corresponding to Ki approximately 1.6 to 10 nanomolar). The antagonism is competitive and surmountable. The functional consequence is suppression of NKB-driven KNDy neuronal firing, restoration of a wider thermoneutral zone, and reduction in the frequency and severity of inappropriate heat-dissipation episodes [2, 9].

The NK3 receptor antagonist mechanism is shared with fezolinetant, the first approved NK3-selective antagonist (Vezoh; Astellas, FDA-approved May 2023). The distinguishing feature of elinzanetant is the concurrent NK1 receptor antagonism [10].

4.3 NK1 receptor antagonism

The NK1 receptor (neurokinin 1 receptor; TACR1 gene product) is a G protein-coupled receptor for substance P, broadly expressed in the central nervous system including the hypothalamus, amygdala, brainstem, and cortex. In the context of KNDy neuronal physiology, substance P acting at NK1 receptors amplifies KNDy excitability and contributes to the dysregulated firing pattern. Beyond the thermoregulatory circuit, NK1 receptor signaling is implicated in sleep regulation, mood, anxiety, and nociception [9, 15].

Elinzanetant binds human NK1 receptors with high affinity (pKi 8.7 to 10.2, corresponding to Ki approximately 0.06 to 2.0 nanomolar), with greater than 300-fold selectivity over non-NK off-target receptors. Cranial imaging studies in humans have demonstrated dose-dependent NK1 receptor occupancy with an EC50 of approximately 0.9 ng/mL plasma concentration [2].

The therapeutic consequence of concurrent NK1 antagonism is additive benefit on sleep disturbance, mood dysregulation, and quality of life beyond what NK3 antagonism alone provides. This is supported by the consistent superiority of elinzanetant over placebo on secondary endpoints of sleep quality and menopause-related quality of life across the OASIS program [11, 12, 13].

4.4 NK2 receptor selectivity

Elinzanetant has minimal activity at the NK2 receptor (pKi approximately 6.0), the primary receptor for neurokinin A in peripheral tissues (gastrointestinal smooth muscle, airways). The greater than 100-fold selectivity for NK1 and NK3 over NK2 predicts the absence of the peripheral gastrointestinal and bronchoconstrictor effects that would accompany non-selective tachykinin receptor antagonism [2].

4.5 Neuroendocrine pharmacodynamics

In Phase 1 studies in healthy premenopausal women, elinzanetant 120 mg daily produced significant reductions in serum estradiol (change of negative 141.4 versus negative 16.5 pmol/L for placebo, p less than 0.05) and luteal-phase progesterone (change of negative 19.4 versus positive 3.18 nmol/L for placebo, p less than 0.05), consistent with modulation of hypothalamic KNDy neuron output to GnRH neurons. Serum luteinizing hormone and follicle-stimulating hormone were not significantly altered, suggesting that the effect on gonadal steroids is mediated through altered GnRH pulsatility rather than gross suppression of gonadotropin secretion [16].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Elinzanetant is rapidly absorbed after oral administration, with a median time to peak plasma concentration (T_{max}) of approximately 1 hour. Absolute oral bioavailability is 52 percent. Within the investigated dose range of 40 to 160 mg, exposure (C_{max} and AUC) increases in a greater-than-dose-proportional manner. Steady-state plasma concentrations are achieved after 5 to 7 days of once-daily dosing. Food effects on absorption have not been reported as clinically significant in the marketed prescribing information; the compound is administered at bedtime without regard to food [2, 4, 19].

5.2 Distribution

Elinzanetant has a large volume of distribution at steady state (V_{ss} approximately 137 L following intravenous administration), reflecting extensive tissue distribution. Plasma protein binding is 99.7 percent, predominantly to albumin and alpha-1-acid glycoprotein. The blood-to-plasma ratio is 0.6 to 0.7, indicating preferential plasma partitioning. The compound crosses the blood-brain barrier, as demonstrated by cranial positron emission tomography imaging studies showing NK1 receptor occupancy in the human brain at therapeutic plasma concentrations [2, 19].

5.3 Metabolism

Elinzanetant is extensively metabolized in the liver, primarily by cytochrome P450 3A4 (CYP3A4), with minor contributions from uridine 5'-diphospho-glucuronosyl-transferase (UGT) conjugation. Three active metabolites (designated M27, M30/34, and M18/21) possess comparable potency at NK1 and NK3 receptors relative to the parent compound. In a human mass balance study, parent elinzanetant accounted for 39.1 percent of total plasma radioactivity; the oxidation product M30/34 was the only metabolite with exposure exceeding 10 percent of total radioactivity (13.7 per-

cent), with M27 at 7.6 percent and M18/21 at 4.9 percent. The aggregate active metabolite exposure is approximately 39 percent of parent plasma concentrations [19, 20].

Elinzanetant is also a weak inhibitor of CYP3A4, a property that produces clinically relevant increases in the exposure of sensitive CYP3A4 substrates when co-administered [4].

5.4 Elimination

The elimination half-life of elinzanetant is approximately 45 hours, supporting once-daily dosing with stable trough concentrations. Systemic clearance following intravenous administration is 8.77 L/h. In a radiolabeled mass balance study, the primary route of excretion was fecal (mean 90.4 percent of total radioactivity), predominantly as metabolites. Urinary recovery was negligible (mean 0.4 percent), indicating that renal excretion is not a meaningful elimination pathway [19, 20].

5.5 Routes of administration

The compound is administered orally as soft capsules containing 60 mg of elinzanetant. The recommended dose is 120 mg (two capsules) once daily at bedtime. No intravenous, intramuscular, or subcutaneous formulations are marketed or in clinical development. Research-grade elinzanetant is supplied as a powder for dissolution in appropriate solvents for in vitro and in vivo investigational applications [4].

5.6 Special populations

Hepatic impairment: Mild hepatic impairment (Child-Pugh A) produces a 1.2-fold increase in C_{max} and a 1.5-fold increase in AUC; no dose adjustment is required. Moderate hepatic impairment (Child-Pugh B) produces a 2.3-fold increase in both C_{max} and AUC; no specific dose adjustment is recommended in the current prescribing information, but clinical monitoring is advised. Severe hepatic impairment (Child-Pugh C) has not been evaluated; elinzanetant is contraindicated in severe hepatic impairment [4].

Renal impairment: Mild to moderate renal impairment does not require dose adjustment. Moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m²) produces 2.3-fold and 2.2-fold increases in unbound C_{max} and AUC, respectively. Severe re-

nal impairment (eGFR less than 30) produces approximately 1.9-fold increases in both parameters. End-stage renal disease (eGFR less than 15) has not been assessed; elinzanetant is not recommended in this population [4].

Pregnancy: Elinzanetant is contraindicated in known or suspected pregnancy. Animal studies demonstrated pregnancy loss and stillbirth at clinically relevant exposures. Females of reproductive potential should be tested for pregnancy before initiating treatment and should use effective contraception during treatment and for 2 weeks after discontinuation [4].

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

Elinzanetant demonstrates high-affinity competitive antagonism at both human NK1 and NK3 receptors in heterologous expression systems. The pKi values at the NK1 receptor range from 8.7 to 10.2 across assay systems (corresponding to Ki approximately 0.06 to 2.0 nanomolar); pKi values at the NK3 receptor range from 8.0 to 8.8 (Ki approximately 1.6 to 10 nanomolar). Selectivity over the NK2 receptor is greater than 100-fold (NK2 pKi approximately 6.0), and selectivity over a panel of greater than 70 off-target receptors, ion channels, and enzymes is greater than 300-fold for NK1 and greater than 100-fold for NK3 [2].

The three principal active metabolites (M27, M30/34, M18/21) exhibit comparable potency at NK1 and NK3 receptors, contributing to the sustained pharmacodynamic effect observed with the long elimination half-life of the parent compound [19].

6.2 In vivo thermoregulatory models

Preclinical characterization of the KNDy neuron thermoregulatory pathway established the rationale for NK3 receptor antagonism in VMS. In the rat, NK3 receptor-expressing neurons in the median preoptic nucleus modulate heat-dissipation effectors; focal microinjection of the NK3 receptor agonist senktide into the median preoptic nucleus reduces core body temperature in the female rat, confirming that NK3 receptor activation drives heat-dissipation pathways [18]. Systemic administration of NK3 receptor antagonists blocks this effect and normalizes thermoregulatory set points in ovariectomized animal models that recapitulate the estrogen-depleted state of menopause.

The additive contribution of NK1 receptor antagonism to the thermoregulatory and behavioral phenotype has been characterized in preclinical models showing that substance P amplifies KNDy neuronal excitability and that combined NK1/NK3 blockade produces broader symptom relief than NK3 antagonism alone, encompassing thermoregulation, sleep architecture, and stress-related behaviors [9].

6.3 Reproductive toxicology

Animal reproductive toxicology studies demonstrated that elinzanetant produces pregnancy loss and stillbirth at exposures approximating clinical levels, consistent with the compound's pharmacological activity on the hypothalamic-pituitary-gonadal axis. These findings are the basis for the contraindication in pregnancy and the requirement for pregnancy testing and contraception in females of reproductive potential [4].

6.4 Seizure signal

Convulsions were observed in animal studies at supratherapeutic exposures. One seizure event was reported in a clinical trial participant with a pre-existing seizure history. The mechanistic basis for the seizure signal is not fully characterized but is plausibly related to modulation of tachykinin signaling in cortical and limbic circuits. The compound should be used with caution in patients with seizure history or conditions that lower the seizure threshold [4].

7. Clinical Evidence Base

7.1 SWITCH-1 (Phase 2b dose-finding)

The SWITCH-1 study was a randomized, double-blind, placebo-controlled, Phase 2b dose-finding trial in postmenopausal women aged 40 to 65 years with moderate-to-severe VMS. Multiple elinzanetant doses were evaluated. At the 120 mg once-daily dose (n equals 52), VMS frequency was reduced by 3.93 per day versus placebo at week 4 (p less than 0.001) and by 2.95 per day versus placebo at week 12 (p equals 0.01). Severity reduction followed a similar trend. The 120 mg dose was selected for Phase 3 development on the basis of the most favorable efficacy-tolerability balance [17].

7.2 OASIS 1 and OASIS 2 (Phase 3, replicate efficacy studies)

OASIS 1 and OASIS 2 were identically designed randomized, double-blind, placebo-controlled Phase 3 trials conducted at multiple sites in North America and Europe. Each trial enrolled approximately 400 postmenopausal women aged 40 to 65 years with moderate-to-severe VMS (defined as 7 or more moderate-to-severe hot flashes per day, or 50 or more per week). Participants were randomized to elinzanetant 120 mg or matching placebo once daily for 12 weeks [11, 12].

Primary endpoints (VMS frequency, least-squares mean change from baseline versus placebo): OASIS 1: week 4, negative 3.29 (p less than 0.001); week 12, negative 3.22 (p less than 0.001). OASIS 2: week 4, negative 3.04 (p less than 0.001); week 12, negative 3.24 (p less than 0.001).

In absolute terms, OASIS 1 participants on elinzanetant reduced VMS frequency by 7.60 per day at week 4 and 8.66 per day at week 12, compared to 4.31 and 5.44 per day on placebo, respectively. OASIS 2 participants on elinzanetant reduced VMS frequency by 8.58 per day at week 4 and 9.72 per day at week 12, compared to 5.54 and 6.48 per day on placebo [11, 12].

Primary endpoints (VMS severity, 3-point scale, least-squares mean change versus placebo): OASIS 1: week 4, negative 0.3 (p less than 0.001); week 12, negative 0.4 (p less than 0.001). OASIS 2: week 4, negative 0.2 (p less than 0.001); week 12, negative 0.3 (p less than 0.001) [11, 12].

Onset of effect: Statistically significant reductions in daily VMS frequency were observed as early as week 1 in both trials (p less than 0.001 versus placebo) [11, 12].

Secondary endpoints: Elinzanetant met key secondary endpoints at week 12 for sleep disturbances (PROMIS Sleep Disturbance Short Form 8b), menopause-related quality of life (MENQOL), and mood, with statistically significant improvements versus placebo in both trials [11, 12].

7.3 OASIS 3 (Phase 3, long-term safety and efficacy)

OASIS 3 was a double-blind, placebo-controlled, randomized Phase 3 trial conducted at 83 sites in North America and Europe from August 2021 to February 2024. The study enrolled 628 postmenopausal women aged 40 to 65 years with moderate-to-severe VMS and randomized them to elinzanetant 120 mg or placebo once daily for 52 weeks [13].

Primary endpoint: VMS frequency reduction at week 12 (least-squares mean change from baseline versus placebo): negative 1.6 per day (p less than 0.0001). In percentage terms, elinzanetant reduced VMS frequency by more than 73 percent from baseline at week 12, compared to 47 percent for placebo [13].

Long-term efficacy: The treatment benefit was maintained through week 50, with sustained reductions in VMS frequency and severity. Sleep disturbance and menopause-related quality of life improvements were maintained through 52 weeks [13].

Long-term safety: No incidence of endometrial hyperplasia or endometrial malignancy was observed over 52 weeks of continuous treatment. No signal of hepatotoxicity was detected. The adverse-event profile was consistent with the shorter-duration OASIS 1 and OASIS 2 trials [13].

7.4 OASIS 4 (Phase 3, breast cancer endocrine therapy population)

OASIS 4 was a randomized, double-blind, placebo-controlled Phase 3 trial in women aged 18 to 70 years experiencing moderate-to-severe VMS secondary to endocrine therapy (aromatase inhibitors or selective estrogen receptor modulators) for hormone receptor-positive breast cancer. Participants were randomized to elinzanetant 120 mg or placebo once daily for 12 weeks, followed by a 12-week open-label extension [14].

Primary endpoints (VMS frequency, least-squares mean change versus placebo): Week 4: negative 3.5 per day (p less than 0.001). Week 12: negative 3.4 per day (p less than 0.001) [14].

Key secondary endpoints (week 12): Sleep disturbance (PROMIS SD SF 8b): significant improvement versus placebo (p less than 0.001). Menopause-specific quality of life (MENQOL): significant improvement versus placebo (p less than 0.001) [14].

The OASIS 4 results are particularly clinically significant because hormonal therapy is contraindicated in this population, making non-hormonal alternatives the only pharmacological option for VMS management. Elinzanetant is the first non-hormonal compound to demonstrate efficacy in this specific population in a Phase 3 trial.

7.5 Population pharmacokinetic-pharmacodynamic modeling

Willmann et al. (2024) published a population pharmacokinetic-pharmacodynamic model integrating Phase 1 and Phase 2 clinical data, demonstrating that elinzanetant plasma concentrations correlated with VMS frequency reduction in a concentration-dependent manner. The model estimated oral bioavailability at 36.7 percent (lower than the 52 percent absolute bioavailability from formal bioavailability studies, reflecting model-specific assumptions), clearance at 7.26 L/h, and central and peripheral distribution volumes of 23.7 and 168 L, respectively [19].

8. Sourcing and Quality Verification

Pharmaceutical-grade elinzanetant (Lynkuet brand) is the highest quality source for research applications. The marketed product is supplied as 60 mg soft capsules for oral administration. Pharmaceutical sourcing is feasible in jurisdictions where the compound is approved (United States, United Kingdom, Australia, Canada, Switzerland, and additional jurisdictions following EMA recommendation) [4].

Research-grade elinzanetant is available from multiple chemical and pharmaceutical research suppliers (BOC Sciences, MedChemExpress, MuseChem, Cayman Chemical, MedKoo, Selleckchem, and others) at greater than 98 percent purity by HPLC. Supply is typically in milligram to gram quantities as the free base. The CAS number 929046-33-3 is the canonical procurement identifier [5].

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ at m/z 669.26 for the protonated free base)
- Nuclear magnetic resonance spectroscopy (1H and ^{19}F NMR) to confirm the bis(trifluoromethyl)phenyl moiety and the hexahydropyrazino-oxazine stereochemistry
- Chiral chromatography or optical rotation measurement to confirm (7S,9aS) stereochemical purity
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical confirmation of vendor certificates of analysis is recommended for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Elinzanetant free base is practically insoluble in water at neutral pH and slightly soluble under acidic conditions. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (typically 10 to 50 mM), which are then diluted into aqueous assay buffers to achieve the desired final concentration. The maximum DMSO concentration in the final assay should not exceed the tolerance of the biological system under study (typically 0.1 to 1.0 percent for cell-based assays).

For in vivo research applications in animal models, formulation in appropriate vehicles (such as polyethylene glycol, hydroxypropyl-beta-cyclodextrin, or methylcellulose suspensions with acidic pH adjustment) may be necessary to achieve adequate oral bioavailability given the compound's limited aqueous solubility.

Storage of the solid compound should be at negative 20 degrees Celsius, desiccated and protected from light. DMSO stock solutions should be stored at negative 20 degrees Celsius in aliquots to minimize freeze-thaw cycles. Stability under these conditions is generally adequate for at least 12 months, though investigators should confirm potency if stock solutions are older than 6 months.

For clinical-research applications, the marketed Lynkuet capsule formulation (60 mg soft capsules) is the appropriate material. The soft capsule formulation contains excipients optimized for oral bioavailability; the capsules should be stored at controlled room temperature (20 to 25 degrees Celsius) and protected from moisture.

10. Stack Interactions and Combinations

Elinzanetant interacts with several drug classes through its CYP3A4-mediated metabolism and through its neurokinin receptor pharmacology. Investigators conducting research with elinzanetant should consider the following interactions:

Strong CYP3A4 inhibitors: Concomitant use with strong CYP3A4 inhibitors (itraconazole, ketoconazole, ritonavir, clarithromycin, cobicistat, nefazodone, posaconazole, voriconazole) is contraindicated. Itraconazole co-administration produces a 3.3-fold increase in elinzanetant C_{max} and a 4.6- to 6.3-fold increase in AUC, substantially exceeding the therapeutic exposure range and increasing the risk of adverse events [4].

Moderate CYP3A4 inhibitors: Concomitant use with moderate CYP3A4 inhibitors (erythromycin, verapamil, diltiazem, fluconazole, ciprofloxacin, aprepitant, cyclosporine) requires dose reduction to 60 mg once daily. Erythromycin co-administration produces a 2.0-fold increase in C_{max} and a 3.0-fold increase in AUC [4].

Weak CYP3A4 inhibitors: Concomitant use with weak CYP3A4 inhibitors (cimetidine) produces a modest 1.3-fold increase in C_{max} and 1.5-fold increase in AUC. No dose adjustment is required, but clinical monitoring may be appropriate in patients receiving multiple weak inhibitors [4].

Strong and moderate CYP3A4 inducers: Concomitant use with strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort) and moderate inducers (efavirenz, bosentan, modafinil) should be avoided, as reduced elinzanetant exposure may compromise therapeutic efficacy [4].

Grapefruit and grapefruit juice: Should be avoided during elinzanetant treatment owing to CYP3A4 inhibition in intestinal enterocytes [4].

Sensitive CYP3A4 substrates: As a weak CYP3A4 inhibitor, elinzanetant increases exposure of co-administered CYP3A4 substrates. Concomitant use with sensitive CYP3A4 substrates with narrow therapeutic indices (such as certain immunosuppressants, antiarrhythmics, or ergot alkaloids) may require dose adjustment or enhanced monitoring of the substrate drug [4].

Hormonal contraceptives: The neuroendocrine effects of elinzanetant (reduction in estradiol and progesterone in premenopausal women) do not affect the efficacy of hormonal contraceptives in the marketed indication (postmenopausal women). However, investigators studying the compound in premenopausal populations should consider potential interactions with hormonal contraceptive efficacy [16].

Other neurokinin receptor antagonists: Concurrent use with aprepitant, fosaprepitant, netupitant, or fezolinetant is pharmacologically redundant for the shared receptor target and may produce additive effects at the overlapping receptor. The combination has not been studied and is not recommended.

Breast cancer endocrine therapies: In the OASIS 4 population, elinzanetant was co-administered with aromatase inhibitors (letrozole, anastrozole, exemestane) and selective estrogen receptor modulators (tamoxifen) without apparent pharmacokinetic or pharmacodynamic interaction that compromised the efficacy of either drug [14].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at the approved 120 mg daily dose, based on pooled data from the OASIS Phase 3 program, are:

- Headache (7.8 percent on elinzanetant versus approximately 5 percent on placebo)
- Fatigue (5.0 percent on elinzanetant versus approximately 3 percent on placebo)
- Dizziness (1 to 10 percent)
- Somnolence (1 to 10 percent)
- Abdominal pain (1 to 10 percent)
- Diarrhea (1 to 10 percent)
- Rash (1 to 10 percent)
- Muscle spasms (1 to 10 percent) [2, 4]

These adverse events are predominantly mild to moderate in severity and are consistent across the 12-week and 52-week study durations.

11.2 Hepatic safety

Elevated hepatic transaminases (ALT, AST) were observed in some clinical trial participants. The prescribing information requires baseline hepatic laboratory testing (ALT, AST, alkaline phosphatase, total bilirubin) before initiation of elinzanetant. The compound should not be started if ALT or AST is 2 times or more the upper limit of normal, or if total bilirubin is 2 times or more the upper limit of normal. Periodic hepatic monitoring is recommended. In the 52-week OASIS 3 study, no signal of clinically significant hepatotoxicity was observed, and no cases of drug-induced liver injury meeting Hy's law criteria were reported [4, 13].

11.3 Endometrial safety

A key safety concern for any non-hormonal therapy in postmenopausal women is endometrial safety. Across the OASIS Phase 3 program, no cases of endometrial hyperplasia or endometrial malignancy were observed over treatment durations up to 52 weeks. This distinguishes elinzanetant from hormonal therapies (unopposed estrogen) that carry established endometrial cancer risk [13].

11.4 Seizure risk

Convulsions were observed in preclinical animal studies. One clinical trial participant with a pre-existing seizure history experienced a seizure event during elinzanetant treatment. The compound should be used with caution in patients with a history of seizures or conditions that lower the seizure threshold (such as concurrent medications that reduce seizure threshold, alcohol withdrawal, or structural brain lesions) [4].

11.5 Pregnancy and reproductive safety

Elinzanetant is contraindicated in known or suspected pregnancy based on animal reproductive toxicology studies demonstrating pregnancy loss and stillbirth. Pregnancy testing is required before initiation; effective contraception is required during treatment and for 2 weeks after discontinuation in females of reproductive potential [4].

11.6 Central nervous system effects

Somnolence, dizziness, and fatigue are reported adverse events that reflect the central nervous system penetration and NK1 receptor occupancy of elinzanetant. The bedtime dosing recommendation is designed to mitigate the functional impact of these effects. Patients should be advised about potential impairment of activities requiring alertness until individual response is characterized [4].

12. Comparative Assessment

This section presents a structured comparative assessment of five alternative compounds for the management of vasomotor symptoms against elinzanetant, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators were selected to represent the principal pharmacological strategies for VMS management, including neurokinin receptor antagonism, selective serotonin and norepinephrine reuptake inhibition, gabapentinoid modulation, and hormonal therapy.

12.1 Fezolinetant (Veoza)

Mechanism: Selective NK3 receptor antagonist. Fezolinetant blocks NK3 receptors on KNDy neurons without concurrent NK1 antagonism, targeting the NKB-mediated thermoregulatory dysregulation specifically [10].

Development trajectory: Developed by Astellas Pharma. Approved by the FDA in May 2023 as the first NK3 receptor antagonist for moderate-to-severe VMS associated with menopause, based on the SKYLIGHT Phase 3 program (SKYLIGHT 1, SKYLIGHT 2, SKYLIGHT 4). The recommended dose is 45 mg orally once daily [10].

Novelty: Moderate. Fezolinetant was the first-in-class NK3 receptor antagonist approved for VMS. However, the selective NK3 mechanism is now considered a subset of the broader neurokinin receptor antagonist approach.

Effect size: In the SKYLIGHT trials, fezolinetant 45 mg produced VMS frequency reductions of approximately 1.4 to 2.5 per day versus placebo at weeks 4 and 12. A systematic review and meta-analysis comparing the two compounds reported a mean difference in 50 percent or greater VMS frequency reduction of negative 1.38 for fezolinetant versus negative 2.04 for elinzanetant, suggesting a numerically larger effect size for elinzanetant [21].

Promising potential: High. The compound is approved and commercially available. Long-term safety data through 52 weeks are available from the SKYLIGHT 4 study. The compound occupies a defined commercial position as the first approved non-hormonal neurokinin-targeted therapy for VMS.

Side-effect profile: The principal safety concern with fezolinetant is hepatotoxicity. The FDA-approved label includes a boxed warning for risk of liver injury, requiring hepatic function testing before, during, and after treatment. This hepatotoxicity signal is more prominent than the hepatic monitoring requirements for elinzanetant, which does not carry a boxed warning [10, 21].

Overall validation: High. Robust Phase 3 data, FDA approval, and commercial availability. However, the hepatotoxicity signal and the absence of NK1-mediated benefits on sleep and mood represent limitations relative to elinzanetant.

Comparison to elinzanetant: Elinzanetant's dual NK1/NK3 mechanism produces broader symptom relief (sleep, mood, quality of life) than fezolinetant's selective NK3 antagonism. Elinzanetant has demonstrated a numerically larger effect size on VMS frequency, faster onset of action, and a more favorable hepatic safety profile (no boxed warning). Fezolinetant has a 2-year head start in commercial availability and longer post-marketing experience.

12.2 Paroxetine (Brisdelle)

Mechanism: Selective serotonin reuptake inhibitor (SSRI). The mechanism of action in VMS is incompletely characterized but is thought to involve modulation of serotonergic neurotransmission in hypothalamic thermoregulatory centers [22].

Development trajectory: Paroxetine mesylate 7.5 mg was approved by the FDA in 2013 as Brisdelle for the treatment of moderate-to-severe VMS associated with menopause. It was the first non-hormonal pharmacotherapy approved for this indication.

Novelty: Low. SSRIs are a well-established drug class; the repositioning for VMS was incremental.

Effect size: Modest. In the pivotal trials, paroxetine 7.5 mg produced VMS frequency reductions of approximately 1.0 to 1.6 per day versus placebo, smaller than the reductions observed with elinzanetant or fezolinetant [22].

Promising potential: Low. The compound is approved and commercially available but has been largely superseded by the neurokinin receptor antagonist class, which produces larger effect sizes with a more targeted mechanism.

Side-effect profile: The SSRI adverse-event profile includes nausea, headache, fatigue, dizziness, and sexual dysfunction. The sexual dysfunction signal is particularly relevant in the menopausal population and distinguishes the SSRI class negatively from the neurokinin antagonist class. Paroxetine also carries a boxed warning for suicidality in young adults [22].

Overall validation: Moderate. FDA-approved with established efficacy, but modest effect size and SSRI-class adverse events limit clinical utility.

Comparison to elinzanetant: Elinzanetant produces substantially larger VMS frequency reductions, has a more targeted mechanism without serotonergic side effects, and provides additional benefits on sleep and quality of life. Paroxetine remains relevant for patients who cannot access neurokinin antagonists or who have concurrent indications for SSRI therapy.

12.3 Venlafaxine

Mechanism: Serotonin-norepinephrine reuptake inhibitor (SNRI). The dual monoaminergic mechanism modulates hypothalamic thermoregulation through both serotonergic and noradrenergic pathways [23].

Development trajectory: Venlafaxine is used off-label for VMS at doses of 37.5 to 150 mg daily. It has not received FDA approval for this indication but is recommended in clinical guidelines as a non-hormonal alternative for VMS management.

Novelty: Low. Off-label use of an established antidepressant.

Effect size: Moderate. Published trials report VMS frequency reductions of approximately 1.5 to 2.5 per day versus placebo at 75 mg daily, comparable to fezolinetant but generally smaller than elinzanetant [23].

Promising potential: Low. No regulatory pathway for VMS indication; use remains off-label.

Side-effect profile: SNRI adverse events include nausea, dry mouth, insomnia, constipation, hypertension, and discontinuation syndrome. Sexual dysfunction is less prevalent than with SSRIs but remains a concern.

Overall validation: Low to moderate. Supported by clinical trial evidence and guideline recommendations for off-label use, but absent formal regulatory approval for VMS.

Comparison to elinzanetant: Elinzanetant provides a more targeted mechanism, larger and more consistent effect sizes, regulatory approval for the VMS indication, and absence of monoaminergic adverse events. Venlafaxine remains a cost-effective off-label option.

12.4 Gabapentin

Mechanism: Voltage-gated calcium channel alpha-2-delta subunit ligand. The mechanism in VMS is thought to involve modulation of hypothalamic neurotransmission and peripheral nociceptive pathways [24].

Development trajectory: Gabapentin is used off-label for VMS at doses of 900 to 2400 mg daily in divided doses. It has not received FDA approval for VMS. Clinical evidence includes several randomized controlled trials in postmenopausal women and in breast cancer patients on endocrine therapy.

Novelty: Low. Off-label use of an established anticonvulsant.

Effect size: Moderate. Published trials report VMS frequency reductions of approximately 1.5 to 2.0 per day versus placebo, with substantial inter-individual variability and dose-dependent sedation that limits tolerability at effective doses [24].

Promising potential: Low. No regulatory pathway for VMS indication.

Side-effect profile: Dose-dependent somnolence, dizziness, peripheral edema, and cognitive blunting. The sedation is the principal tolerability limitation and limits up-titration to effective analgesic and VMS doses.

Overall validation: Low to moderate. Supported by randomized trial evidence for off-label use. Widely available and inexpensive.

Comparison to elinzanetant: Elinzanetant provides a more targeted mechanism, regulatory approval, larger effect sizes, and a more favorable tolerability profile. Gabapentin may be preferred in patients with concurrent neuropathic pain or insomnia who benefit from the sedative properties.

12.5 Conjugated estrogens/bazedoxifene (Duavee)

Mechanism: Tissue-selective estrogen complex. Conjugated estrogens provide estrogen replacement to restore hypothalamic thermoregulatory set points; bazedoxifene (a selective estrogen receptor modulator) antagonizes estrogen activity at the endometrium to prevent endometrial hyperplasia without requiring concurrent progestin [25].

Development trajectory: Approved by the FDA in 2013 for moderate-to-severe VMS and prevention of postmenopausal osteoporosis in women with an intact uterus. The combination avoids the need for concomitant progestogen that is required with conventional estrogen replacement therapy.

Novelty: Moderate. The tissue-selective approach was innovative at the time of approval but remains fundamentally hormonal.

Effect size: Large. Hormonal therapy is the most effective pharmacological intervention for VMS, with VMS frequency reductions of 70 to 90 percent from baseline in clinical trials, generally exceeding the effect sizes of non-hormonal alternatives including elinzanetant [25].

Promising potential: Moderate. Commercially available and clinically effective, but restricted to populations without contraindications to hormonal therapy (excludes women with hormone receptor-positive breast cancer, history of venous thromboembolism, cardiovascular disease, or personal preference against hormones).

Side-effect profile: The estrogen component carries established risks of venous thromboembolism, stroke, and breast cancer with prolonged use (Women's Health Initiative data). Bazedoxifene mitigates endometrial risk but does not eliminate the systemic estrogen-associated cardiovascular and oncological risks.

Overall validation: High for efficacy. The limitations are safety-driven rather than efficacy-driven.

Comparison to elinzanetant: Conjugated estrogens/bazedoxifene produces larger VMS reductions than elinzanetant but carries cardiovascular and oncological risks that make it unsuitable for substantial patient populations. Elinzanetant provides a non-hormonal alternative with clinically meaningful efficacy, a favorable safety profile, and applicability to populations in whom hormonal therapy is contraindicated (including breast cancer endocrine therapy patients).

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the VMS treatment landscape. **Fezolinetant** is the closest mechanistic comparator, sharing the NK3 antagonist mechanism but lacking NK1 activity; it provides a single-receptor alternative with a more prominent hepatotoxicity signal. **Paroxetine** is the first approved non-hormonal therapy but produces modest effect sizes with SSRI-class adverse events. **Venlafaxine** is a commonly used off-label alternative with moderate effect sizes and monoaminergic adverse events. **Gabapentin** is an inexpensive off-label option limited by sedation and cognitive effects. **Conjugated estrogens/bazedoxifene** is the most effective therapy for VMS but is restricted by hormonal safety concerns.

Elinzanetant occupies a distinctive position as the only approved dual NK1/NK3 receptor antagonist, combining the thermoregulatory benefits of NK3 antagonism with the sleep, mood, and quality-of-life benefits of NK1 antagonism. The compound produces clinically meaningful VMS reductions (73 percent from baseline at 12 weeks in OASIS 3), rapid onset (week 1), sustained efficacy (52 weeks), and a favorable safety profile without the hepatotoxicity boxed warning of fezolinetant, the serotonergic/noradrenergic adverse events of SSRIs and SNRIs, the sedation of gabapentinoids, or the cardiovascular and oncological risks of hormonal therapy. For populations in whom hormonal therapy is contraindicated (particularly breast cancer endocrine therapy patients, as demonstrated in OASIS 4), elinzanetant represents the most comprehensively validated non-hormonal pharmacological option currently available.

13. References

1. te Beek ET, Hay JL, Bullman JN, et al. Pharmacokinetics and central nervous system effects of the novel dual NK1/NK3 receptor antagonist GSK1144814 in alcohol-intoxicated volunteers. *Br J Clin Pharmacol*. 2013;75(5):1328-1339.
2. Markham A. Elinzanetant: first approval. *Drugs*. 2025. doi:10.1007/s40265-025-02244-3.
3. Simon JA, Anderson RA, Ballantyne E, et al. Elinzanetant, a new combined neurokinin-1/-3 receptor antagonist for the treatment of postmenopausal vasomotor symptoms. *Expert Opin Pharmacother*. 2024;25(8):1007-1018.
4. Bayer HealthCare Pharmaceuticals. LYNKUET (elinzanetant) capsules, for oral use: US prescribing information. Silver Spring, MD: US Food and Drug Administration; October 2025.
5. PubChem. Elinzanetant. National Center for Biotechnology Information. PubChem Compound CID 16063568.
6. Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flashes. *Front Neuroendocrinol*. 2013;34(3):211-227.
7. Padilla SL, Johnson CW, Barker FD, Patterson MA, Palmiter RD. A neural circuit underlying the generation of hot flashes. *Cell Rep*. 2018;24(2):271-277.
8. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, et al. Arcuate kisspeptin/neurokinin B/dynorphin (KNDy) neurons mediate the estrogen suppression of gonadotropin secretion and body weight. *Endocrinology*. 2012;153(6):2800-2812.
9. Depypere H, Lademacher C, Gerlinger C, et al. The combined neurokinin-1 and neurokinin-3 receptor antagonist elinzanetant for vasomotor symptoms: mechanistic rationale and clinical evidence. *Climacteric*. 2024;27(3):231-239.
10. Fraser GL, Lederman S, Engber T, et al. Fezolinetant, a neurokinin-3 receptor antagonist, for the treatment of vasomotor symptoms in postmenopausal women. *Maturitas*. 2023;175:107773.

11. Lederman S, Ottery FD, Cano A, et al. Elinzanetant for vasomotor symptoms associated with menopause: OASIS 1 and OASIS 2 phase 3 randomized clinical trials. *JAMA*. 2024;332(5):400-411.
12. Bayer AG. Results from Phase III duo show elinzanetant significantly reduced frequency and severity of hot flashes associated with menopause. Press release. 2024.
13. Simon JA, Depypere H, Engel S, et al. Elinzanetant for the treatment of vasomotor symptoms associated with menopause: a phase 3 randomized clinical trial (OASIS 3). *JAMA Intern Med*. 2025;185(10):1165-1174.
14. Bayer AG. Elinzanetant meets all primary and secondary endpoints in Phase III study OASIS 4 for treatment of moderate to severe vasomotor symptoms caused by breast cancer treatments. Press release. 2024.
15. Quartara L, Maggi CA. The tachykinin NK1 receptor. Part II: distribution and pathophysiological roles. *Neuropeptides*. 1998;32(1):1-49.
16. Prague JK, Roberts RE, Comninou AN, et al. Elinzanetant (NT-814), a neurokinin 1,3 receptor antagonist, reduces estradiol and progesterone in healthy women. *J Clin Endocrinol Metab*. 2021;106(9):e3574-e3585.
17. Trower M, Anderson RA, Sheridan B, et al. Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1). *Menopause*. 2023;30(3):239-246.
18. Krajewski-Hall SJ, Blackmore EM, McMinn JR, Rance NE. Neurokinin 3 receptor-expressing neurons in the median preoptic nucleus modulate heat-dissipation effectors in the female rat. *Endocrinology*. 2015;156(8):2552-2562.
19. Willmann S, Thelen K, Kubitza D, et al. Population pharmacokinetic-pharmacodynamic model of elinzanetant based on integrated clinical phase I and II data. *CPT Pharmacometrics Syst Pharmacol*. 2024;13(12):2120-2132.
20. Garner CR, Gotta V, Garg A, et al. Mass balance recovery, absorption, metabolism, and excretion of elinzanetant in healthy human volunteers and in vitro biotransformation. *Eur J Drug Metab Pharmacokinet*. 2025;50(1):89-101.
21. Li Y, Chen X, Wang J, et al. Efficacy and safety of fezolinetant and elinzanetant for vasomotor symptoms in postmenopausal women: a systematic review and meta-analysis. *Maturitas*. 2025;193:108148.

22. Stearns V, Beebe KL, Iyengar M, Dube E. Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. JAMA. 2003;289(21):2827-2834.
23. Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. Lancet. 2000;356(9247):2059-2063.
24. Guttuso T Jr, Kurlan R, McDermott MP, Kieburztz K. Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstet Gynecol. 2003;101(2):337-345.
25. Pinkerton JV, Harvey JA, Lindsay R, et al. Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial. J Clin Endocrinol Metab. 2014;99(2):E189-E198.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Elinzanetant (Lynkuet) is approved by the United States Food and Drug Administration for the treatment of moderate-to-severe vasomotor symptoms due to menopause. Investigators should consult their local regulatory authority and the current prescribing information before any research application. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.