

## Drug Update-Elinzanetant

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### Abstract

Elinzanetant is a dual neurokinin-1 (NK1) and neurokinin-3 (NK3) receptor antagonist currently in development for the treatment of vasomotor symptoms (VMS)—such as hot flashes and night sweats—in postmenopausal women. It exerts its therapeutic effect by blocking NK3 receptors, thereby inhibiting neurokinin B (NKB) activity on KNDy neurons in the hypothalamus, which are involved in thermoregulation.

Elinzanetant has shown consistent efficacy and safety across two Phase II and four Phase III clinical trials, demonstrating its potential in treating moderate to severe VMS associated with menopause as well as those induced by adjuvant endocrine therapy.

**Keywords:** Menopause; Vasomotor Symptoms; Hot Flashes, Neurokinin.

### INTRODUCTION

**Elinzanetant**, also known as **NT-814**, is an investigational medication being developed to treat **vasomotor symptoms (VMS)** such as **hot flashes** and **night sweats** in postmenopausal women. In premenopausal women, it has been shown to suppress levels of **luteinizing hormone, estradiol, and progesterone** in a dose-dependent manner. Elinzanetant belongs to a novel class of drugs that act as **dual antagonists of neurokinin NK1 and NK3 receptors**. Its development is currently being led by **Bayer**, in collaboration with **GlaxoSmithKline** and **NeRR Therapeutics**<sup>1</sup>.

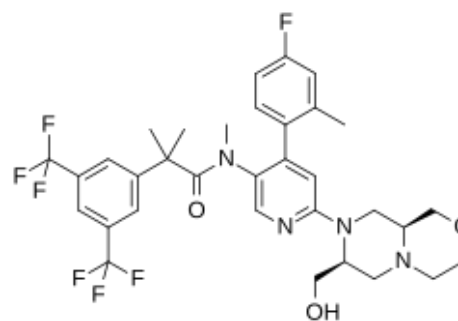
**Elinzanetant** is the first **dual neurokinin-1 (NK1) and neurokinin-3 (NK3) receptor antagonist** in late-stage clinical development for the **non-hormonal, once-daily oral treatment of moderate-to-severe vasomotor symptoms (VMS)** associated with menopause. It targets the underlying pathophysiology of VMS by modulating **KNDy neurons**—a group of estrogen-sensitive neurons in the hypothalamus. With declining estrogen levels during menopause, these neurons become hypertrophic and trigger **hyperactivation of the thermoregulatory pathway**, leading to impaired body temperature control and the onset of VMS. In addition to reducing hot flashes and night sweats, elinzanetant may also help alleviate **menopause-related sleep disturbances**. Elinzanetant may also decrease sleep disturbances associated with menopause<sup>1,2</sup>.

### About Vasomotor Symptoms

Vasomotor symptoms (VMS) commonly known as hot flashes are driven by the hyperactivation of the thermoregulatory pathway, a process mediated by the hypertrophy of KNDy neurons in the hypothalamus. This neuronal change is triggered by a decline in estrogen levels, which may occur naturally during menopause or as a result of medical interventions such as bilateral oophorectomy or endocrine therapy. In women undergoing endocrine therapy for the treatment or prevention of breast cancer, VMS are a common and distressing side effect, significantly affecting quality of life and treatment adherence. Currently, no approved therapies exist for managing VMS in this patient population.

**Menopause** is a natural transitional phase in a woman's life, marked by the **progressive decline of ovarian function**, typically occurring in the **late 40s to early 50s**. It can also result from **medical or surgical interventions**, such as treatments for **breast cancer**. The associated **hormonal decline** particularly in estrogen can trigger a range of symptoms that may significantly impact a woman's **health, quality of life, healthcare utilization, and work productivity**. Among the most commonly reported and disruptive symptoms during the menopausal transition are **vasomotor symptoms (VMS), sleep disturbances and mood changes**<sup>1</sup>.

### CHEMICAL STRUCTURE



Molecular formula: C<sub>33</sub>H<sub>35</sub>F<sub>7</sub>N<sub>4</sub>O<sub>3</sub>

MW: 668.6 g/mol

IUPAC Name: *N*-[6-[(7*S*,9*aS*)-7-(hydroxymethyl)-3,4,6,7,9,9*a*-hexahydro-1*H*-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

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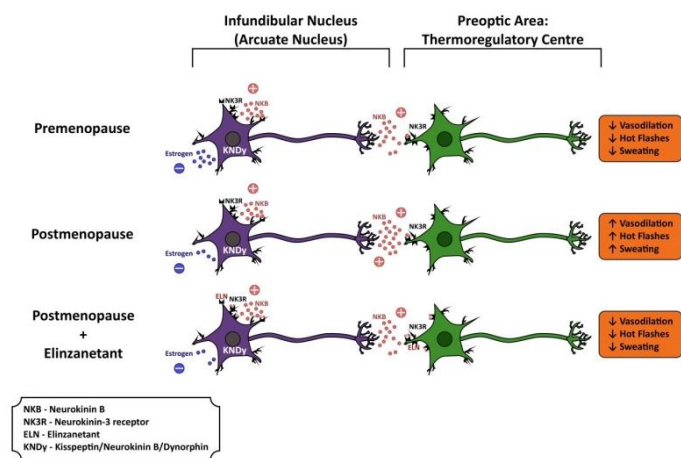
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## MECHANISM OF ACTION



**Figure 1:** Mechanism of action of Elinzanetant

Elinzanetant is a non-hormonal therapy currently in development for the treatment of vasomotor symptoms (VMS) associated with menopause. It acts as a dual antagonist of neurokinin-1 (NK1) and neurokinin-3 (NK3) receptors, specifically targeting mechanisms involved in thermoregulation. Within the hypothalamus, KNDy neurons—which co-express kisspeptin, neurokinin B (NKB) and dynorphin—play a key role in regulating body temperature. During menopause, the decline in estrogen leads to hyperactivation of KNDy neurons, disrupting thermoregulatory control and resulting in symptoms such as hot flashes.

Elinzanetant works by blocking NK3 receptors, thereby inhibiting NKB activity on KNDy neurons and helping to restore thermoregulatory balance. The additional antagonism of NK1 receptors may enhance efficacy by further reducing vasodilation and heat-sensing neuronal activity, offering potential advantages over NK3 receptor antagonism alone<sup>2</sup>.

## DOSE

Therapeutic dose of elinzanetant is 120 mg once daily administration.

## PHARMACOKINETICS

**Elinzanetant** is **rapidly absorbed** following oral administration, with an **elimination half-life ( $t_{1/2}$ ) of approximately 35 hours**. With **once-daily dosing**, **steady-state concentrations** are typically reached within **5 to 7 days** and drug accumulation remains **modest (<2-fold)**. Elinzanetant is primarily **metabolized by the cytochrome P450 enzyme CYP3A4**. Its **systemic clearance** is estimated at **7.26 L/h**, with a **central distribution volume** of **23.7 L** and a **peripheral distribution volume** of **168 L**. Co-administration with **high-fat meals** has been shown to **reduce the absorption rate** of elinzanetant<sup>6</sup>.

## ADVERSE EVENT AND TOLERABILITY

Elinzanetant was well tolerated in clinical trial phase-II and III with minimal side effects. The most common

adverse drug reaction (ADR) in elinzanetant group was mild somnolence, Headache, fatigue and arthralgia. No severe adverse event was reported<sup>4</sup>.

## CLINICAL TRIALS

Two phase II clinical trials namely the RELENT-1 study (NCT02865538), (n=76) and the SWITCH-1 study (NCT03596762), (n=199) were performed on premenopausal women. The RELENT-1 study, received elinzanetant or placebo for 14 days in the doses of 50 mg/100 mg/150 mg/300 mg per day orally. Improvements in hot flash frequency, severity, and severity score were greatest in the 150 mg (84%) and 300 mg (66%) groups compared to placebo and 50 mg groups. The most common adverse events were mild somnolence and headaches, followed by diarrhea and pelvic pain. The rate of adverse events was highest in the 300 mg dose group. In the SWITCH-1 study, Elinzanetant/placebo was given for 12 weeks in the doses of 120 mg/160 mg per day. The Insomnia Severity Index questionnaire (ISI), the Pittsburgh Sleep Quality Index (PSQI) total score, and the Menopause-specific Quality-of-Life questionnaire intervention (MenQol-I) were used for assessment of sleep and quality of life. Clinically meaningful improvements in ISI, PSQI and MenQol-I were observed in the 120 mg and 160 mg groups at weeks 4, 8, 12, and 16<sup>2,7</sup>.

The Phase III CT specifically OASIS program, currently comprises four Phase III studies: OASIS 1, 2, 3 and 4. OASIS 1 and 2 (NCT05042362 and NCT05099159), (n=396 and 400 respectively) investigated the efficacy and safety of elinzanetant for 26 weeks in the dose of 120 mg orally once daily or matching placebo for 12 weeks followed by elinzanetant, 120 mg, for 14 weeks. In both trials, reductions in VMS frequency and severity from baseline to weeks 4 and 12 were statistically significantly greater for elinzanetant vs placebo group<sup>4</sup>. The **OASIS 3 trial** (NCT05030584), which included **628 participants**, evaluated the **long-term safety and efficacy of elinzanetant over 52 weeks**. The results were **consistent with previous findings**, further supporting its **favorable safety profile**. Notably, there were **no reported cases of endometrial hyperplasia or endometrial malignant neoplasms**, and **no signals of hepatotoxicity** were observed during the study<sup>8</sup>. The phase 3 OASIS 4 (NCT05030584) study for 52 weeks, demonstrated that elinzanetant, significantly reduced the frequency and severity of moderate to severe vasomotor symptoms (VMS) in women undergoing adjuvant endocrine therapy for hormone receptor-positive breast cancer. Improved sleep quality and menopause-related quality of life were reported by participants from baseline to weeks 4 and 12 compared with placebo. Elinzanetant's safety profile remained consistent, supporting its potential as a nonhormonal treatment option for managing VMS<sup>9</sup>.

## Abbreviations

ISI	: Insomnia Severity Index questionnaire
MW	: Molecular Weight
MenQoI-I	: Menopause-specific Quality-of-Life questionnaire intervention
NK	: Neurokinin
PSQI	: Pittsburgh Sleep Quality Index
VMS	: Vasomotor symptoms

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## Availability of data and materials

Data will be available by emailing shubhasharmajpr@gmail.com

## Authors' Contributions

- Author1: Literature search, writing, and editing.
- Author2: Reviewing, and editing

All authors have read and agreed to the published version of the manuscript. All authors have read the final manuscript.

## Competing Interest

The authors declare that they have no competing interests.

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