

MINI REVIEW

Neurokinin 1/3 Receptor Antagonists for Vasomotor Symptoms in Women with Breast Cancer

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Endocrine therapy remains a cornerstone treatment for patients with hormone receptor-positive breast cancer. However, its benefits are often undermined by treatment-related adverse events, including vasomotor symptoms (VMS) such as hot flashes and night sweats. These symptoms can substantially impair quality of life and contribute to poor treatment adherence, thereby reducing the effectiveness of endocrine therapy and potentially increasing the risk of disease recurrence. While hormone replacement therapy is effective for managing postmenopausal hot flashes in the general population, it is contraindicated in women receiving endocrine, essentially an anti-estrogen, breast cancer treatment. Therefore, safe and effective non-hormonal strategies are required. Traditional pharmaceutical options, such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin and clonidine, provide modest benefit but are often limited by their own side effects or drug-drug interactions with endocrine therapies. More recently, targeted approaches using neurokinin receptor antagonists, including fezolinetant and elinzanetant, have shown promise in reducing the frequency and severity of VMS. This review highlights the rationale, evidence and clinical potential of neurokinin receptor antagonists as emerging non-hormonal options for managing breast cancer-related VMS.

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Introduction

Vasomotor symptoms (VMS), primarily hot flashes and night sweats, are among the most frequent and burdensome side effects in women with breast cancer, particularly those receiving endocrine therapy.¹⁻⁴ Compared with symptoms associated with natural menopause, treatment-induced VMS may be more abrupt, severe and are strongly associated with non-adherence or discontinuation of therapy.^{3,5-7} Effective management is therefore essential, not only to alleviate symptoms and improve quality of life (QoL) but also to support adherence to life-prolonging endocrine treatments.

Because hormone replacement therapy is contraindicated in patients with estrogen receptor-positive disease due to concerns about cancer recurrence, safe and effective non-hormonal strategies are needed.⁴ Current initial approaches include non-pharmacological options, with cognitive behavioral therapy demonstrating the strongest evidence, as well as pharmacological agents that provide only modest benefit.

In recent years, novel agents targeting the neural pathways underlying VMS have been investigated in clinical trials for the treatment of moderate-to-severe postmenopausal symptoms. These include the neurokinin (NK) receptor antagonists fezolinetant, elinzanetant, pavinetant (MLE4901), osanetant (ACER-801) and SJX-653. Of these, fezolinetant and elinzanetant are now approved in Switzerland^{8,9} and the European Union^{10,11} for the treatment of moderate-to-severe VMS in postmenopausal women. Despite initially positive trial results, the development of pavinetant was discontinued in 2017 due to safety concerns.^{12,13} Both osanetant (ACER-801) and SJX-653 failed to demonstrate efficacy in phase II trials.¹⁴⁻¹⁶

This review summarizes traditional non-hormonal pharmacological options and outlines the mechanistic rationale for neurokinin receptor antagonism. It also evaluates current evidence on the efficacy and safety of neurokinin receptor antagonists in managing VMS, with a focus on breast cancer-related VMS, and explores their potential role in standard supportive care.

Traditional non-hormonal pharmacological agents

Non-hormonal pharmacological options for the management of VMS include antidepressants, such as selective serotonin reuptake inhibitors (SSRI) (e.g., escitalopram) and selective norepinephrine reuptake inhibitors (SNRI) (e.g., venlafaxine), as well as antihypertensive medications (clonidine) and anticonvulsants (gabapentin). These medications provide only mild-to-moderate relief from hot flashes and are often limited by tolerability concerns.

Table 1. Key non-hormonal pharmacologic agents previously studied for the management of vasomotor symptoms in women with a history of breast cancer.

Agent	Class	Outcome in VMS	Safety
Venlafaxine ¹⁹	SNRI	58% reduction for 150 mg/d and 46% reduction for 75 mg/d vs 19% with placebo (for 4 weeks; $p<0.001$)	Generally well tolerated; dry mouth, decreased appetite, nausea and constipation more frequent compared with placebo
Paroxetine ²⁰	SSRI	40.6% reduction (10 mg/d) vs 13.7% with placebo ($p=0.0006$) 51.7% reduction (20 mg/d) vs 26.6% with placebo ($p=0.002$)	Most AEs mild; withdrawal more common with 20 mg dose, mostly due to drowsiness and nausea Avoid with tamoxifen
Gabapentin ²¹	GABA analog	At weeks 4 ($p=0.0001$) and 8 ($p=0.007$): 49% reduction and 46% for 900 mg vs 33% reduction and 31% for 300 mg vs 21% reduction and 15% for placebo	Withdrawal mostly due to somnolence or fatigue
Clonidine ²⁴	α_2 -adrenergic agonist	37% vs 20% with placebo at week 4 ($p=0.001$) 38% vs 24% with placebo at week 8 ($p=0.006$)	Difficulty sleeping
Oxybutynin ²³	Anticholinergic drug	77% reduction for 5 mg BID ($p<0.001$) and 60% for 2.5 mg BID ($p=0.002$) vs 27% for placebo (for 6 weeks)	Increased mouth dryness, constipation, difficulty urinating

Results shown as % of reduction in hot flash frequency. AE, adverse event; BID, twice a day; d, day; GABA, γ -aminobutyric acid; SNRI, selective norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors.

Reported adverse events occur in approximately 80% of patients.^{17,18} [Table 1](#) summarizes key agents used for VMS management and their reported outcomes in clinical studies.¹⁹⁻²³

Mechanistic rationale of neurokinin receptor antagonism

The hypothalamic-pituitary-ovarian (HPO) axis regulates female reproductive function through pulsatile secretion of gonadotropin-releasing hormone (GnRH), which stimulates the anterior pituitary to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH).²⁵ Elevated FSH and LH promote estrogen production by the ovaries, which establishes a negative feedback loop that suppresses further GnRH release.

Postmortem studies have identified hypertrophy of specialized neurons in the hypothalamic arcuate nucleus that co-express kisspeptin, neurokinin B and dynorphin (Dyn).²⁶ These so-called KNDy neurons are estrogen-sensitive and play a central role in regulating the pulsatile release of GnRH; kisspeptin stimulates GnRH secretion, while neurokinin B provides stimulatory modulation and Dyn exerts inhibitory control.^{12,26,27} Under normal conditions, estrogen suppresses KNDy neuron activity. However, during estrogen deficiency, as occurs in natural menopause or under endocrine therapy, neurokinin B signaling is increased via the neurokinin-3 receptor (NK3R). The KNDy neurons also project to warmth-sensing areas in the medial preoptic nucleus, a key center for thermoregulation. Excessive neurokinin B signaling in this pathway contributes to thermoregulatory instability, resulting in cutaneous vasodilation and the clinical manifestation of VMS.¹²

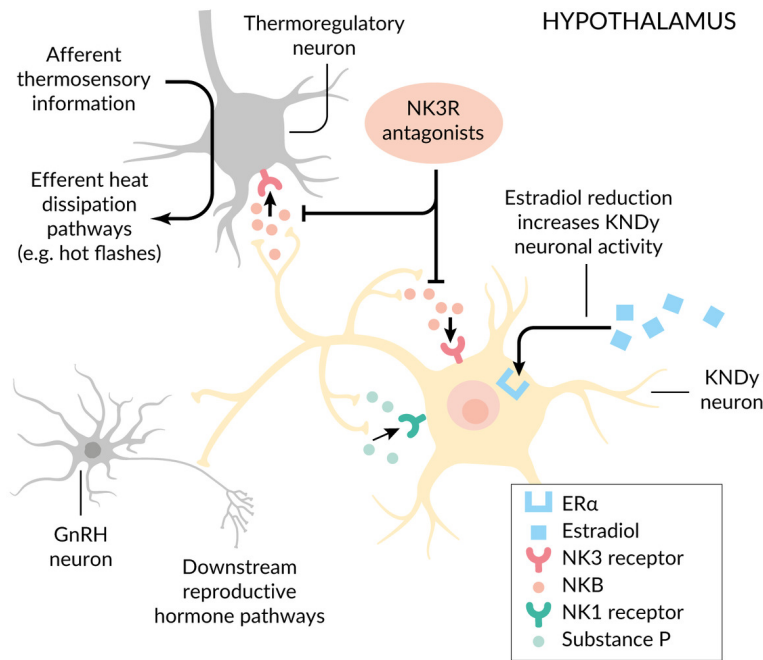


Figure 1. Mechanistic rationale of neurokinin receptor antagonists in the treatment of vasomotor symptoms.

GnRH, gonadotropin-releasing hormone; ERα, estrogen receptor alpha; NKB, neurokinin B; NK1, neurokinin 1; NK3, neurokinin 3. Adapted from Comninos and Dhillon 2023³⁰ and Sassarini and Anderson 2024.³¹

KNDy neurons express both NK1 and NK3 receptors, as well as their respective ligands, substance P and neurokinin B. Estrogen deficiency induces hypertrophy and hyperactivity of these neurons, accompanied by elevated expression of both neurokinin B and substance P.^{26,28} This dysregulation disrupts thermoregulatory homeostasis and is considered a central mechanism in the onset of VMS.²⁹

Figure 1 illustrates the mechanistic rationale for the use of neurokinin receptor antagonists in the treatment of VMS. These agents act by targeting the tachykinin system, particularly substance P signaling through NK1 and neurokinin B signaling through NK3 receptors, within the hypothalamic thermoregulatory center, thereby stabilizing temperature control and reducing the frequency of hot flashes.

Clinical development of neurokinin receptor antagonists

Following the identification of KNDy neurons as key mediators in the development of VMS, neurokinin receptors emerged as promising therapeutic targets. Fezolinetant, a selective NK3 receptor antagonist, demonstrated significant efficacy in reducing hot-flash frequency in two similar phase III studies involving a total of 1,022 women experiencing menopause. In the SKYLIGHT 1 study, once-daily fezolinetant 45 mg achieved a 61% reduction in hot-flash frequency by week 12, compared with a 35% reduction with placebo ($p < 0.001$).³² In the SKYLIGHT 2 trial, the

Table 2. Efficacy and safety of neurokinin receptor antagonists in the treatment of menopause-associated vasomotor symptoms (VMS) in key clinical trials.

Agent	Clinical Trial	Frequency	Severity	TEAEs in the 12-Week Placebo-Controlled Period (vs Placebo)
Fezolinetant ^{*,†}	SKYLIGHT ¹³²	-2.55 (SE: 0.43; p<0.001)	-0.20 (SE: 0.08; p=0.007)	43% vs 45%
	SKYLIGHT ²³³	-2.53 (SE: 0.55; p<0.001)	-0.29 (SE: 0.08; p<0.001)	35.9% vs 32.3%
Elinzanetant ^{**,‡}	OASIS 1 ³⁴	-3.2 (95% CI: -4.8 to -1.6; p<0.001)	-0.4 (95% CI: -0.5 to -0.3; p<0.001)	51.3% vs 48.5%
	OASIS 2 ³⁴	-3.2 (95% CI: -4.6 to -1.9; p<0.001)	-0.3 (95% CI: -0.4 to -0.1; p<0.001)	44.3% vs 38.2%
	OASIS-4 ³⁵	Week 4: -3.5 (95% CI: -7.2 to -5.8; p<0.001) Week 12: -3.4 (95% CI: -4.2 to -2.5; p<0.001)	Week 4: -0.73 vs -0.43 (placebo) Week 12: -0.98 vs -0.53 (placebo)	NA

Mean change in daily frequency and severity of moderate-to-severe VMS from baseline to week 12 was analyzed as least-squares (LS) mean difference versus placebo, except for severity in OASIS-4, where mean change from baseline is reported for elinzanetant versus placebo. NA, not available; SE, standard error; TEAEs, treatment-emergent adverse events.

*at a daily dose of 45 mg (recommended⁸); †monitoring liver function is recommended due to risk of drug-induced liver injury⁸; **at a daily dose of 120 mg;

‡OASIS-4 specifically studied elinzanetant in women receiving endocrine therapy for breast cancer.

same regimen reduced hot flashes by 64% versus 45% with placebo by week 12.³³ Both studies also showed reductions in symptom severity, with benefits maintained for up to one year ([Table 2](#)).^{32,33}

The randomized, placebo-controlled, double-blind, dose-ranging VESTA study further demonstrated that fezolinetant compared with placebo improved quality of life (QoL) and patient-reported outcomes, including decreased interference of VMS with daily activities and better menopause-related QoL scores.³⁶ A recent meta-analysis of five randomized clinical trials (n=2,168) reported a 22.5% greater mean reduction in VMS frequency with fezolinetant versus placebo, along with modest improvements in menopause-related QoL, particularly sleep quality.³⁷ Moreover, a 2024 network meta-analysis of pooled data from phase III fezolinetant trials plus 23 comparator studies confirmed that fezolinetant 45 mg reduced VMS frequency with efficacy comparable to hormone therapy and superior to other non-hormonal agents.³⁸

Elinzanetant is a dual neurokinin 1/3 receptor antagonist developed for the treatment of VMS.³¹ In the phase III OASIS 1 and OASIS 2 trials conducted over 26 weeks in women experiencing menopause-related VMS, elinzanetant significantly reduced the frequency and severity of moderate-to-severe VMS compared with placebo ([Table 2](#)).³⁴ The treatment also led to greater improvements in sleep disturbances and menopause-related QoL. These benefits were sustained in the OASIS 3 trial, which confirmed efficacy over 52 weeks.³⁹

The phase III OASIS-4 trial is the first study to specifically evaluate the efficacy and safety of elinzanetant (120 mg daily) in women with or at high risk for hormone receptor (HR)-positive breast cancer experiencing endocrine therapy-associated VMS.³⁵ Women were randomly assigned in a 2:1 ratio to receive elinzanetant for 52 weeks (n=316) or placebo for 12 weeks (n=158) followed by elinzanetant for 40 weeks. The primary endpoints were the change in mean daily frequency of moderate-to-severe VMS from baseline to weeks 4 and 12. At baseline, the mean daily frequency of moderate-to-severe VMS was 11.4 episodes in the elinzanetant arm and 11.5 episodes in the placebo arm. At week 4, elinzanetant reduced VMS frequency by -6.5 episodes versus -3.0 with placebo, corresponding to a least-squares mean difference of -3.5 ($p<0.001$). At week 12, reductions were -7.8 versus -4.2 episodes, yielding a difference of -3.4 ($p<0.001$). Elinzanetant also demonstrated significant benefits in key secondary endpoints, including improvements in sleep quality as measured by the Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form (PROMIS SD SF) and in overall menopause-related quality of life as assessed by the Menopause-Specific Quality of Life (MENQOL) questionnaire.

Safety and tolerability

Overall, neurokinin receptor antagonists are considered safe in treating menopausal VMS.^{34-36,40,41} While some adverse events have been reported, they are often mild and manageable, with a low incidence of serious side effects.

In the large, 52-week safety study SKYLIGHT 4, treatment-emergent adverse events (TEAEs) with fezolinetant were generally mild to moderate in severity, with low rates of fezolinetant discontinuation (fezolinetant 30 mg, 5.6%; fezolinetant 45 mg, 4.6%; placebo, 4.3%).⁴⁰ The overall incidence of TEAE was similar across groups: 67.9% with fezolinetant 30 mg, 63.9% with fezolinetant 45 mg and 64.1% with placebo. Elevations in liver enzymes greater than three times the upper limit of normal (ULN) were rare and no cases fulfilled Hy's law criteria (*i.e.*, no severe drug-induced liver injury with alanine aminotransferase [ALT] or aspartate aminotransferase [AST] more than three times the ULN and total bilirubin more than two times the ULN, with no elevation of alkaline phosphatase and no other reason to explain the combination); therefore, they were not considered clinically relevant. With respect to endometrial safety, one patient in the fezolinetant 45-mg group developed endometrial hyperplasia, while no cases were reported in the placebo or fezolinetant 30-mg groups. Endometrial malignancy was observed in one patient in the 30-mg group, with no cases in the other treatment arms.

In a pooled analysis of the SKYLIGHT 1, 2 and 4 trials, the incidence of severe TEAEs was 3.5% with fezolinetant 45 mg compared with 2.5% with placebo.⁴¹ Serious drug-related TEAEs were reported in four patients

receiving fezolinetant 45 mg (0.4%). TEAEs of special interest with fezolinetant include elevations in ALT and AST, which are mostly mild and transient.^{32,33} Although no cases of severe drug-induced liver injury were observed, the occurrence of liver enzyme elevations greater than three times the ULN led regulatory agencies to recommend routine liver function monitoring.^{8,10,41,42} The ongoing phase III HIGHLIGHT 1 trial is further assessing the safety or efficacy of fezolinetant in women with breast cancer receiving adjuvant endocrine therapy.⁴³

Similarly, elinzanetant has demonstrated a favorable safety profile in the OASIS 1 and OASIS 2 studies, with the most frequent TEAEs being headache (7.0–9.0%) and fatigue (5.5%–7.0%) and no cases of liver injury reported.³⁴ There were no cases of endometrial hyperplasia or malignant neoplasm in either trial.

In the OASIS-4 trial in women with severe VMS receiving endocrine therapy for breast cancer, most AEs with elinzanetant were mild or moderate, with severe events reported in 4.1% of patients.³⁵ Serious AEs were uncommon, occurring in 2.5% of patients receiving elinzanetant versus 0.6% with placebo. During weeks 1 to 12, somnolence, fatigue and diarrhea were reported more frequently with elinzanetant than with placebo. Elevations in liver enzymes requiring monitoring were observed in five patients (including one serious case), all in the elinzanetant group; however, none met Hy's law criteria. Between weeks 13 and 52, a small number of cancer-related events were recorded: one patient developed a new breast cancer, one experienced recurrence and one progressed to stage IV disease; in addition, one patient had suspected liver metastasis and one developed bone and liver metastases.

Managing VMS in women with breast cancer

Management of VMS in women with breast cancer requires a structured approach to improve QoL and support adherence to endocrine therapy ([Figure 2](#)). The initial evaluation should include assessment of symptom burden using the Menopause Rating Scale II (MRS II),^{44,45} impact on daily functioning and exclusion of alternative causes. First-line strategies comprise lifestyle and supportive measures, including patient education, behavioral strategies and exercise. If symptoms persist, treatment may be escalated to hormonal agents, such as elinzanetant or fezolinetant. Other parallel treatment options include non-hormonal agents such as SSRIs, SNRIs, gabapentin or clonidine, with careful monitoring for side effects and potential drug interactions. Long-term management requires regular reassessment of VMS severity, treatment tolerability and adherence, timely therapeutic adjustments and continued patient education to maintain both symptom control and adherence to breast cancer therapy. Treatment duration depends on the symptom burden of the patient and modifications during endocrine

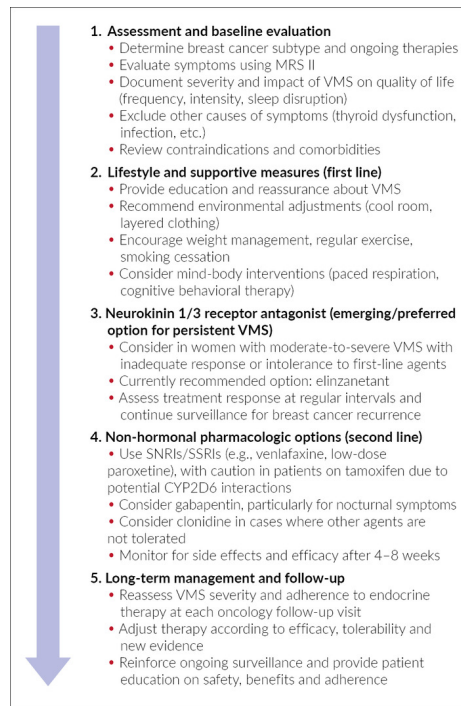


Figure 2. Suggested treatment algorithm for managing vasomotor symptoms (VMS) in women with breast cancer.

MRS II, Menopause Rating Scale II; SNRIs, selective serotonin reuptake inhibitors; SSRIs, serotonin norepinephrine reuptake inhibitors.

therapy course are needed regularly. In OASIS-4, elinzanetant was administered for 52 weeks.³⁵ As long-term follow-up is not yet available, the length of therapy should be discussed and individualized with each patient.

Conclusion

Neurokinin receptor antagonists represent a major advance in the non-hormonal management of VMS, providing effective and well-tolerated relief. For women with breast cancer, these agents may address a critical gap in supportive care. Beyond symptom reduction, their use has the potential to improve adherence to endocrine therapy by alleviating one of the most common causes of treatment discontinuation, thereby contributing to better survival outcomes and highlighting their broader clinical significance. Both fezolinetant and elinzanetant have demonstrated compelling efficacy for the treatment of moderate-to-severe VMS; however, further research is needed to establish their role, including head-to-head comparisons with existing nonhormonal therapies, dedicated trials in breast cancer populations and rigorous long-term safety evaluation. Addressing these evidence gaps will be essential to support their integration into standard survivorship care pathways for women with HR-positive breast cancer.

Conflict of interest

Michael Gnant reports receiving personal fees and/or travel support from Amgen, AstraZeneca, Bayer, Daiichi Sankyo, Eli Lilly, EPG Health (IQVIA), Menarini-Stemline, MSD, Novartis, Pierre Fabre and Veracyte; he also holds leadership roles at ABCSG GmbH and ABCSG Research Services GmbH. Marcus Vetter received honoraria for consultancy from GSK, Roche, Novartis, ExactSciences, Pfizer, Stemline, AbbVie and ASC Oncology. Petra Stute serves on advisory boards for Astellas and Bayer and gives lectures at congresses supported by these companies. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

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REFERENCES

1. Biglia N, Cozzarella M, Cacciari F, et al. Menopause after breast cancer: a survey on breast cancer survivors. *Maturitas*. 2003;45(1):29-38. doi:[10.1016/S0378-5122\(03\)00087-2](https://doi.org/10.1016/S0378-5122(03)00087-2)
2. Berkowitz MJ, Thompson CK, Zibecchi LT, et al. How patients experience endocrine therapy for breast cancer: an online survey of side effects, adherence, and medical team support. *J Cancer Surviv*. 2021;15(1):29-39. doi:[10.1007/s11764-020-00908-5](https://doi.org/10.1007/s11764-020-00908-5)
3. Zhu L, Hsieh TT, Iyer TK, Morgans AK, Hamnvik OR. Management of vasomotor symptoms in cancer patients. *Oncologist*. 2025;30(2):oyaf002. doi:[10.1093/oncolo/oyaf002](https://doi.org/10.1093/oncolo/oyaf002)
4. Hickey M, Basu P, Sassarini J, et al. Managing menopause after cancer. *Lancet*. 2024;403(10430):984-996. doi:[10.1016/S0140-6736\(23\)02802-7](https://doi.org/10.1016/S0140-6736(23)02802-7)
5. Avis NE, Crawford SL, Green R. Vasomotor Symptoms Across the Menopause Transition: Differences Among Women. *Obstet Gynecol Clin North Am*. 2018;45(4):629-640. doi:[10.1016/j.ogc.2018.07.005](https://doi.org/10.1016/j.ogc.2018.07.005)
6. Cole KM, Clemons M, Alzahrani M, et al. Vasomotor symptoms in early breast cancer-a “real world” exploration of the patient experience. *Support Care Cancer*. 2022;30(5):4437-4446. doi:[10.1007/s00520-022-06848-3](https://doi.org/10.1007/s00520-022-06848-3)
7. Kingsberg S, Banks V, Caetano C, et al. Treatment utilization and non-drug interventions for vasomotor symptoms in breast cancer survivors taking endocrine therapy: Real-world findings from the United States and Europe. *Maturitas*. 2024;188:108071. doi:[10.1016/j.maturitas.2024.108071](https://doi.org/10.1016/j.maturitas.2024.108071)
8. VEOZA™ (fezolinetant). Information for healthcare professionals. Swissmedic. 2025. Accessed August 2025. <https://swissmedicinfo.ch/>
9. LYNKUET® (elinzanetant). Information for healthcare professionals. Swissmedic. 2025. Accessed August 2025. <https://swissmedicinfo.ch/>
10. VEOZA® (fezolinetant). Summary of product characteristics. The European Medicines Agency. 2023. Accessed August 2025. https://www.ema.europa.eu/en/documents/product-information/veoza-epar-product-information_en.pdf
11. LYNKUET® (elinzanetant). The European Medicines Agency 2025. Summary of product characteristics. Accessed August 2025. <https://www.ema.europa.eu/en/medicines/human/EPAR/lynkuet>
12. Prague JK, Roberts RE, Comninou AN, et al. Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flashes: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;389(10081):1809-1820. doi:[10.1016/s0140-6736\(17\)30823-1](https://doi.org/10.1016/s0140-6736(17)30823-1)
13. Pavinetant. Inxight Drugs. Accessed August 2025. <https://drugs.ncats.io/substances?q=%22pavinetant%22&facet=Substance%20Form%2FPrincipal%20Form>
14. Acer Therapeutics. Corporate presentation 2023. Accessed August 2025. <https://www.acertx.com/wp-content/uploads/2023/03/Acer-Corporate-Presentation-3-27-23-final.pdf>
15. Dose-ranging, PK, Safety, Efficacy Study of Osanetant in Patients With Moderate/Severe VMS Associated With Menopause. National Library of Medicine. Accessed August 2025. <https://www.clinicaltrials.gov/study/NCT05325775>
16. Phase 2 Study of SJX-653 in Postmenopausal Women With Moderate to Severe Vasomotor Symptoms. National Library of Medicine. Accessed August 2025. <http://www.clinicaltrials.gov/study/NCT04278872>

17. Rada G, Capurro D, Pantoja T, et al. Non-hormonal interventions for hot flashes in women with a history of breast cancer. *Cochrane Database of Syst Rev*. 2010;(9):CD004923. doi:[10.1002/14651858.CD004923.pub2](https://doi.org/10.1002/14651858.CD004923.pub2)
18. Hervik JB, Stub T. Adverse effects of non-hormonal pharmacological interventions in breast cancer survivors, suffering from hot flashes: A systematic review and meta-analysis. *Breast Cancer Res Treat*. 2016;160(2):223-236. doi:[10.1007/s10549-016-4002-x](https://doi.org/10.1007/s10549-016-4002-x)
19. 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. doi:[10.1016/s0140-6736\(00\)03403-6](https://doi.org/10.1016/s0140-6736(00)03403-6)
20. Stearns V, Slack R, Greep N, et al. Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol*. 2005;23(28):6919-6930. doi:[10.1200/jco.2005.10.081](https://doi.org/10.1200/jco.2005.10.081)
21. Pandya KJ, Morrow GR, Roscoe JA, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet*. 2005;366(9488):818-824. doi:[10.1016/s0140-6736\(05\)67215-7](https://doi.org/10.1016/s0140-6736(05)67215-7)
22. Pandya KJ, Raubertas RF, Flynn PJ, et al. Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. *Ann Intern Med*. 2000;132(10):788-793. doi:[10.7326/0003-4819-132-10-200005160-00004](https://doi.org/10.7326/0003-4819-132-10-200005160-00004)
23. Leon-Ferre RA, Novotny PJ, Wolfe EG, et al. Oxybutynin vs Placebo for Hot Flashes in Women With or Without Breast Cancer: A Randomized, Double-Blind Clinical Trial (ACCRU SC-1603). *JNCI Cancer Spectr*. 2020;4(1):pkz088. doi:[10.1093/jncics/pkz088](https://doi.org/10.1093/jncics/pkz088)
24. Goldberg RM, Loprinzi CL, O'Fallon JR, et al. Transdermal clonidine for ameliorating tamoxifen-induced hot flashes. *J Clin Oncol*. 1994;12(1):155-158. doi:[10.1200/jco.1994.12.1.155](https://doi.org/10.1200/jco.1994.12.1.155)
25. Limonta P, Marelli MM, Moretti R, Marzagalli M, Fontana F, Maggi R. Chapter Two - GnRH in the Human Female Reproductive Axis. *Vitam Horm*. 2018;107:27-66. doi:[10.1016/bs.vh.2018.01.003](https://doi.org/10.1016/bs.vh.2018.01.003)
26. 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. doi:[10.1016/j.yfrne.2013.07.003](https://doi.org/10.1016/j.yfrne.2013.07.003)
27. Modi M, Dhillon WS. Neurokinin 3 Receptor Antagonism: A Novel Treatment for Menopausal Hot Flashes. *Neuroendocrinol*. 2019;109(3):242-248. doi:[10.1159/000495889](https://doi.org/10.1159/000495889)
28. Navarro VM, Gottsch ML, Chavkin C, Okamura H, Clifton DK, Steiner RA. Regulation of gonadotropin-releasing hormone secretion by kisspeptin/dynorphin/neurokinin B neurons in the arcuate nucleus of the mouse. *J Neurosci*. 2009;29(38):11859-11866. doi:[10.1523/jneurosci.1569-09.2009](https://doi.org/10.1523/jneurosci.1569-09.2009)
29. Zhang Z, Park JW, Ahn IS, et al. Estrogen receptor alpha in the brain mediates tamoxifen-induced changes in physiology in mice. *Elife*. 2021;10:e63333. doi:[10.7554/eLife.63333](https://doi.org/10.7554/eLife.63333)
30. Comninos AN, Dhillon WS. Neurokinin 3 receptor antagonism for menopausal hot flashes. *Cell*. 2023;186(16):3332-3332.e1. doi:[10.1016/j.cell.2023.07.011](https://doi.org/10.1016/j.cell.2023.07.011)
31. Sassarini J, Anderson RA. Elinzanetant: a phase III therapy for postmenopausal patients with vasomotor symptoms. *Expert Opin Investig Drugs*. 2024;33(1):19-26. doi:[10.1080/13543784.2024.2305122](https://doi.org/10.1080/13543784.2024.2305122)

32. Lederman S, Ottery FD, Cano A, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet*. 2023;401(10382):1091-1102. doi:[10.1016/s0140-6736\(23\)00085-5](https://doi.org/10.1016/s0140-6736(23)00085-5)
33. Johnson KA, Martin N, Nappi RE, et al. Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated With Menopause: A Phase 3 RCT. *J Clin Endocrinol Metab*. 2023;108(8):1981-1997. doi:[10.1210/clinem/dgad058](https://doi.org/10.1210/clinem/dgad058)
34. Pinkerton JV, Simon JA, Joffe H, et al. Elinzanetant for the Treatment of Vasomotor Symptoms Associated With Menopause: OASIS 1 and 2 Randomized Clinical Trials. *JAMA*. 2024;332(16):1343-1354. doi:[10.1001/jama.2024.14618](https://doi.org/10.1001/jama.2024.14618)
35. Cardoso F, Parke S, Brennan DJ, et al. Elinzanetant for Vasomotor Symptoms from Endocrine Therapy for Breast Cancer. *N Engl J Med*. 2025;393(8):753-763. doi:[10.1056/NEJMoa2415566](https://doi.org/10.1056/NEJMoa2415566)
36. Santoro N, Waldbaum A, Lederman S, et al. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). *Menopause*. 2020;27(12):1350-1356. doi:[10.1097/gme.0000000000001621](https://doi.org/10.1097/gme.0000000000001621)
37. Bonga KN, Mishra A, Maiti R, Padhy BM, Meher BR, Srinivasan A. Efficacy and Safety of Fezolinetant for the Treatment of Menopause-Associated Vasomotor Symptoms: A Meta-analysis. *Obstet Gynecol*. 2024;143(3):393-402. doi:[10.1097/aog.0000000000005508](https://doi.org/10.1097/aog.0000000000005508)
38. Morga A, Ajmera M, Gao E, et al. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. *Menopause*. 2024;31(1):68-76. doi:[10.1097/gme.0000000000002281](https://doi.org/10.1097/gme.0000000000002281)
39. Panay N, Joffe H, Maki P, et al. Efficacy and long-term safety of elinzanetant for the treatment of VMS associated with menopause: a phase 3 randomized trial (OASIS 3). In: *Proceedings and Abstracts of the 2024 Annual Meeting of the Menopause Society, September 11–14, 2024*. Menopause Society; 2024. <https://menopause.org/wp-content/uploads/2024/09/2024-Oral-and-Poster-Presentation-Abstracts.pdf>
40. Neal-Perry G, Cano A, Lederman S, et al. Safety of Fezolinetant for Vasomotor Symptoms Associated With Menopause: A Randomized Controlled Trial. *Obstet Gynecol*. 2023;141(4):737-747. doi:[10.1097/aog.0000000000005114](https://doi.org/10.1097/aog.0000000000005114)
41. Kagan R, Cano A, Nappi RE, et al. Safety of Fezolinetant for Treatment of Moderate to Severe Vasomotor Symptoms Due to Menopause: Pooled Analysis of Three Randomized Phase 3 Studies. *Adv Ther*. 2025;42(2):1147-1164. doi:[10.1007/s12325-024-03073-8](https://doi.org/10.1007/s12325-024-03073-8)
42. VEOZA™ (fezolinetant). U.S. Food and Drug Administration. 2025. Accessed August 2025. <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>
43. Astellas Initiates Phase 3 Clinical Study of Fezolinetant for VMS in Women with Breast Cancer Receiving Adjuvant Endocrine Therapy. Accessed August 2025. <https://newsroom.astellas.com/2024-08-27-Astellas-Initiates-Phase-3-Clinical-Study-of-Fezolinetant-for-VMS-in-Women-with-Breast-Cancer-Receiving-Adjuvant-Endocrine-Therapy>
44. Honermann L, Knabben L, Weidlinger S, Bitterlich N, Stute P. An extended Menopause Rating Scale II: a retrospective data analysis. *Climacteric*. 2020;23(6):608-613. doi:[10.1080/13697137.2020.1775808](https://doi.org/10.1080/13697137.2020.1775808)
45. Heinemann K, Ruebig A, Potthoff P, et al. The Menopause Rating Scale (MRS) scale: a methodological review. *Health Qual Life Outcomes*. 2004;2:45. doi:[10.1186/1477-7525-2-45](https://doi.org/10.1186/1477-7525-2-45)