

Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause

Background and Scope

June 28, 2022

ICER recognizes that gender language is evolving and that individuals experiencing menopause may have diverse gender identities. In this report, when we use the word “woman” (and the pronouns “she” and “her”) we are describing adult individuals whose biologic sex is female, whether they identify as female, male, or non-binary, among others. When referencing study populations used in specific research studies, we will use the gender language used by the study investigators. As gender language continues to evolve, ICER will periodically reassess this language and make appropriate adjustments as necessary in future versions of this and other reports.

Background

Eighty percent of women undergoing menopause experience vasomotor symptoms (VMS). VMS, characterized by hot flashes and night sweats, are thought to be brought on by decreased estrogen levels and increased neurokinin B (NKB) activity acting on the hypothalamus, a region of the brain which regulates body temperature.¹⁻³ The change in hypothalamic thermoregulation increases blood flow to the skin, resulting in the VMS. Hot flashes are the sudden onset of heat in the upper chest and face which spreads throughout the body, and they typically last two to four minutes. Hot flashes are often accompanied by profuse sweating and, when this occurs at night (night sweats), can cause sleep disruption, and negatively affect mood. Additionally, the combination of vasodilation and sweating can rapidly lower body temperature and cause shivering.

The frequency of VMS varies from one per day to one per hour. Most women who have them experience several per day. The intensity of VMS can be classified as mild (sensation of heat without sweating), moderate (sensation of heat with sweating but able to continue activity), or severe (sensation of heat with sweating, causing cessation of activity). Risk factors for developing vasomotor symptoms include obesity, smoking, reduced physical activity, high follicle-stimulating hormone (FSH) levels, and mutations in the tachykinin receptor 3 gene, which encodes the NKB receptor.^{4,5}

The median duration of vasomotor symptoms is 7.4 years^{6,7} with approximately 40% of women having VMS lasting over 10 years.⁸ Black women typically have the longest duration of symptoms compared to white women while Chinese women typically have the shortest duration of symptoms.^{8,9} More limited evidence suggests that Native American women may have the highest prevalence of VMS.¹⁰

Frequent (7 or more) moderate to severe VMS episodes per day are associated with interference with sleep (94%), concentration (84%), mood (85%), energy (77%), and sexual activity (61%).¹¹ Vasomotor symptoms are estimated to increase direct healthcare costs by \$1,300 per person per year compared to women without these symptoms, and increase indirect economic costs due to missed work by another \$770 per person per year.¹²

Treatment options vary based on symptom severity. Women with mild VMS symptoms are recommended to try behavioral approaches, such as lowering ambient temperature, dressing in layers of clothing, and avoiding physical and emotional triggers (e.g., spicy foods and stressful situations). For women with moderate to severe VMS and no contraindications, menopausal hormone therapy (MHT), consisting of estrogen and a progestin or progesterone (for women with an intact uterus) or estrogen alone (for women who have undergone a hysterectomy) is recommended as first-line therapy. Contraindications to MHT include a history of breast cancer, coronary heart disease, venous thromboembolic (VTE) event or stroke, active liver disease, unexplained vaginal bleeding, high-risk endometrial cancer, or transient ischemic attack¹³, since MHT can potentially increase the risk of these adverse outcomes among older women. Women with high cardiovascular disease risk or moderate to high risk for breast cancer are recommended to try nonhormonal therapies over MHT.

Because some women cannot or do not want to take MHT, nonhormonal therapies have been studied for the treatment of VMS. Antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) can be used to treat VMS. While paroxetine is the only antidepressant with an FDA-approved indication for VMS¹⁴, other SSRIs and SNRIs have also been shown to be effective in reducing symptoms.^{15,16} Further, paroxetine is not recommended for women on tamoxifen, a selective estrogen receptor modulator used to treat breast cancer. Gabapentin and pregabalin are often recommended for women with VMS who also have sleep disturbances as they can aid sleep.

Complementary and alternative therapies have also been studied for the management of VMS, including mind-body therapies such as cognitive behavioral therapy, yoga, exercise, and acupuncture, and natural products such as isoflavones, phytoestrogens, and black cohosh.¹⁷⁻¹⁹ However, the evidence for the effectiveness of these treatments is, at best, inconclusive²⁰, due to heterogeneity between trials and low-quality evidence.¹⁸

Fezolinetant (Astellas Pharma Inc.) is a once daily oral nonhormonal therapy being investigated for the treatment of moderate to severe VMS associated with menopause. It acts by regulating neuronal activity in the hypothalamus thereby affecting temperature regulation. If approved, it would be the first selective neurokinin-3 (NK3) receptor antagonist available in the US. On June 23rd, 2022, Astellas submitted a New Drug Application for fezolinetant to the FDA.²¹

Stakeholder Input

This Revised Scoping Document was developed with input from diverse stakeholders, including patient representatives, clinicians, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders, open input submissions from the public, and feedback on the Draft Scope. Major changes include the need for additional treatment options for VMS and the need for individualized decision making due to the diversity of experience of VMS. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

The majority of women experience VMS associated with menopause. Patient groups, clinical experts, and manufacturers all discussed how impactful VMS can be on a woman's life, disrupting their sleep, mood, cognitive function, ability to work, social life, and overall quality of life. For most women, symptoms tend to attenuate over time and most women stop taking treatments after months to a few years. However, some women have hot flashes lasting for up to 10-20 years. Additionally, while the prevalence of VMS varies by sociodemographic factors, that variation in prevalence decreases during the menopausal transition since most women experience symptoms.

In terms of treatment for VMS, up to 70% of women with moderate-to-severe symptoms may not be adequately treated.¹² Black women, in particular, may experience reduced access to care for VMS due to multiple reasons including lower income, lack of insurance coverage, rurality, transportation constraints, and racism. Furthermore, patient groups, clinicians and manufacturers all discussed the importance of shared decision-making during treatment selection, taking into account individualized risk/benefit profiles and individual goals and preferences. Such an individualized approach is also supported by clinical guidelines.^{22,23}

In discussions with clinical experts, we heard that VMS is undertreated, in part due to the lack of clinicians with expertise in treating menopause symptoms. Furthermore, they highlighted that the heightened risk of cardiovascular disease with estrogen and progestin seen in the Women's Health Initiative (WHI) study may not generalize to treatment of VMS given that treatment tends to start at a younger age and be of shorter duration than in the WHI.²⁴ However, for a subset of women, the duration of VMS can last long enough (10-20 years), that the risks of MHT eventually outweigh the benefits.²⁵ Thus, safe and effective nonhormonal treatment options are an important need. Finally, we heard that while the FDA guidance for industry on clinical evaluation is to include women with 7

to 8 moderate-to-severe hot flashes per day,²⁶ this is a small percentage of the women who experience VMS, so clinical trial results may not necessarily be applicable to women whose symptoms are not as severe.

Report Aim

This project will evaluate the health and economic outcomes of fezolinetant for vasomotor symptoms associated with menopause. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms – including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs – are considered in the judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's [grey literature policy](#)).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (<https://osf.io/7awvd/>).

Populations

The population of focus for the review is women seeking relief from vasomotor symptoms associated with menopause.

Data permitting, we will evaluate the evidence for subpopulations defined by:

- Sociodemographic factors (e.g., age, race, and ethnicity)
- Weight/Body mass index (BMI)
- Women who are not eligible for menopausal hormone therapy due to contraindications (e.g., history of breast cancer, blood clots etc.)
- Women who have experienced surgical menopause

Interventions

The intervention of interest for this review is

- Fezolinetant (Astellas Pharma Inc.)

Comparators

Data permitting, we intend to compare fezolinetant to:

- No medical therapy (as estimated by the placebo arm of clinical trials)
- Menopausal Hormone Therapy
 - Estrogen and progestin or progesterone
 - Estrogen only
- SSRIs/SNRIs
- Gabapentin
- Pregabalin

Outcomes

Data permitting, we will evaluate the outcomes described in the list below.

- Patient-Important Outcomes
 - Frequency and severity of vasomotor symptoms
 - Sleep quality
 - Quality of life
 - Interference of symptoms with daily life
 - Functional impairment (e.g., work productivity)
 - Urogenital menopausal symptoms that may be addressed by the intervention or comparators
 - Other patient-reported outcomes (e.g., mood changes)

- Adverse events (AEs) including but not limited to
 - Serious AEs
 - Discontinuation due to AEs
 - Other AEs including but not limited to
 - Endometrial hyperplasia or cancer
 - Bone density markers (e.g., fractures, osteoporosis)
 - Breast cancer
 - Coronary heart disease
 - Venous thromboembolism (e.g., pulmonary embolism)
 - Stroke
 - Colorectal cancer
 - Liver toxicity (e.g., AST and ALT levels)
 - All-cause mortality
 - Suicidality

Timing

Evidence on intervention effectiveness and evidence on harms will be derived from studies of any duration.

Settings

Vasomotor symptoms associated with menopause are generally treated in outpatient and/or clinic settings, which will be the focus of our review.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients’ ability to achieve major life goals related to education, work, or family life
Caregivers’ quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients’ ability to manage and sustain treatment given the complexity of regimen
Society’s goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of fezolinetant relative to no medical therapy (as estimated by the placebo arms of clinical trials) and to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of menopause. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than \$200,000 per QALY, and/or when the result crosses the threshold of \$100,000 - \$150,000 per QALY gained. The target population will consist of women with VMS associated with menopause. The model will consist of health states that define symptom relief and may include a range of longer-term health outcomes given available evidence. A cohort of patients will transition between states during predetermined cycles of length tied to clinical trial duration over a lifetime time horizon, modeling patients from treatment initiation until death. We will explore treatment durations that are defined by average duration of VMS. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using evidence from trials of fezolinetant trials and relevant comparators derived from the clinical effectiveness section.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of symptom improvements (e.g., using the Menopause-Specific Quality of Life (MENQOL) Questionnaire), life-years gained, quality-adjusted life years (QALYs) gained, and equal

value of life years ([evLYs](#)) gained. Quality-of-life weights will be applied to each health state, including quality-of-life decrements for reasons such as serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the incremental cost per QALY gained, cost per evLY gained, and cost per day with symptom improvement.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found [here](#).

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's [Value Assessment Framework](#)). These services are ones that would not be directly affected by fezolinetant (e.g., prescription of other medications for VMS), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of vasomotor symptoms beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. 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.
2. Jayasena CN, Comninou AN, Stefanopoulou E, et al. Neurokinin B Administration Induces Hot Flashes in Women. *Sci Rep*. 2015;5(1):8466.
3. Skorupskaite K, George JT, Veldhuis JD, Millar RP, Anderson RA. Neurokinin 3 Receptor Antagonism Reveals Roles for Neurokinin B in the Regulation of Gonadotropin Secretion and Hot Flashes in Postmenopausal Women. *Neuroendocrinology*. 2018;106(2):148-157.
4. Gold EB, Colvin A, Avis N, et al. Longitudinal Analysis of the Association Between Vasomotor Symptoms and Race/Ethnicity Across the Menopausal Transition: Study of Women's Health Across the Nation. *American Journal of Public Health*. 2006;96(7):1226-1235.
5. Gold EB, Sternfeld B, Kelsey JL, et al. Relation of Demographic and Lifestyle Factors to Symptoms in a Multi-Racial/Ethnic Population of Women 40–55 Years of Age. *American Journal of Epidemiology*. 2000;152(5):463-473.
6. KRONENBERG F. Hot Flashes: Epidemiology and Physiology. *Annals of the New York Academy of Sciences*. 1990;592(1):52-86.
7. Randolph JF, Jr, Sowers M, Bondarenko I, et al. The Relationship of Longitudinal Change in Reproductive Hormones and Vasomotor Symptoms during the Menopausal Transition. *The Journal of Clinical Endocrinology & Metabolism*. 2005;90(11):6106-6112.
8. Avis NE, Crawford SL, Greendale G, et al. Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition. *JAMA Internal Medicine*. 2015;175(4):531-539.
9. Tepper PG, Brooks MM, Randolph JF, Jr., et al. Characterizing the trajectories of vasomotor symptoms across the menopausal transition. *Menopause*. 2016;23(10):1067-1074.
10. Reed SD, Lampe JW, Qu C, et al. Premenopausal vasomotor symptoms in an ethnically diverse population. *Menopause*. 2014;21(2):153-158.
11. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas*. 2009;62(2):153-159.
12. Sarrel P, Portman D, Lefebvre P, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. *Menopause*. 2015;22(3):260-266.
13. Stuenkel CA, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015;100(11):3975-4011.
14. Administration FaD. BRISDELLE® (paroxetine) Prescribing Information. Food and Drug Administration (FDA). https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204516s003lbl.pdf. Published 1992. Accessed 2022.
15. A.P. H, Williams M. The efficacy and tolerability of SSRI/SNRIs in the treatment of vasomotor symptoms in menopausal women: a systematic review. *Journal of the American Association of Nurse Practitioners*. 2015;27(1):54-61.
16. Shams T, Firwana B, Habib F, et al. SSRIs for Hot Flashes: A Systematic Review and Meta-Analysis of Randomized Trials. *Journal of general internal medicine*. 2013;29(1):204-213.

17. Chiu HY, Pan CH, Shyu YK, Han BC, Tsai PS. Effects of acupuncture on menopause-related symptoms and quality of life in women in natural menopause: a meta-analysis of randomized controlled trials. *Menopause*. 2015;22(2):234-244.
18. Cramer H, Peng W, Launche R. Yoga for menopausal symptoms—A systematic review and meta-analysis. *Maturitas*. 2018;109:13-25.
19. Ye M, Shou M, Zhang j, et al. Efficacy of cognitive therapy and behavior therapy for menopausal symptoms: a systematic review and meta-analysis. *Psychological Medicine*. 2022;52:433-445.
20. Pockaj BA, Gallagher JG, Loprinzi CL, et al. Phase III Double-Blind, Randomized, Placebo-Controlled Crossover Trial of Black Cohosh in the Management of Hot Flashes: NCCTG Trial N01CC. *Journal of Clinical Oncology*. 2006;24(18):2836-2841.
21. Astellas Submits Fezolinetant New Drug Application to U.S. FDA [press release]. June 23rd, 2022 2022.
22. Shifren JL, Gass MLS. The North American Menopause Society Recommendations for Clinical Care of Midlife Women. *Menopause*. 2014;21(10):1038-1062.
23. Crawford SL, Crandall CJ, Derby CA, et al. Menopausal hormone therapy trends before versus after 2002: impact of the Women's Health Initiative Study Results. *Menopause*. 2018;26(6):588-597.
24. Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women Principal Results From the Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2002;288(3):321-333.
25. Brunner RL, Aragaki A, Barnabei V, et al. Menopausal symptom experience before and after stopping estrogen therapy in the Women's Health Initiative randomized, placebo-controlled trial. *Menopause*. 2010;17(5):946-954.
26. Administration FaD. *Guidance for Industry: Estrogen and Estrogen/Progestin Drug Products to Treat Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms — Recommendations for Clinical Evaluation*. 2003.