

KEY FINDINGS

	Evidence Rating	Health-Benefit Price Benchmark
fezolinetant	<p>P/I: Promising but inconclusive when compared to no pharmacologic treatment</p> <p>I: Insufficient compared to menopausal hormone therapy</p>	\$2,000 – \$2,600 per year for women who cannot or choose not to take menopausal hormone therapy

“While menopause is a part of normal aging for women, symptoms associated with menopause can last years and be disruptive. Vasomotor symptoms include flushing and sweating, and when frequent and/or severe, or when sleep is affected, can harm quality of life. Menopausal hormone therapy (MHT) can often effectively treat symptoms of menopause including vasomotor symptoms, but some women have contraindications to MHT and others are concerned about side effects of MHT, including an increased risk of breast cancer. There is an important need for new effective and safe options. While fezolinetant appears to be a promising treatment for women who cannot or do not wish to take MHT, there are still uncertainties about the magnitude of the benefit it provides and its long-term safety. All of the fezolinetant Phase III trials need to be peer reviewed and published.”

– ICER’s Chief Medical Officer, David Rind, MD

THEMES AND RECOMMENDATIONS

- All stakeholders have a responsibility to ensure that women have equitable access to effective new treatment options for symptoms of menopause.
- Payers should use evidence to create coverage criteria for fezolinetant that reflect whether drug pricing is in fair alignment with its benefits to patients.
- Manufacturers should seek to set prices that will foster affordability and access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of new non-hormonal treatments for menopause, there is considerable optimism about emerging therapies, but there is also considerable uncertainty about longer-term safety and effectiveness especially in the case of first-in-class medications. Manufacturer pricing should reflect these considerations in their initial pricing.
- Clinical societies should update treatment guidelines for patients seeking treatment for symptoms of menopause to reflect newly available treatment options.

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Vasomotor symptoms (VMS), namely hot flashes and night sweats, are the hallmark symptoms of menopause. The vast majority of women undergoing menopause experience some degree of VMS, but a substantial proportion experience VMS that are severe enough to impair quality of life or interfere with normal activities. In addition, VMS have both direct healthcare costs and indirect economic costs due to missed work. VMS duration and severity are also known to differ by race and ethnicity, with Black women experiencing the highest burden of VMS.

A number of therapeutics (e.g., anti-depressants, gabapentinoids) have been investigated to treat VMS, with Menopausal Hormone Therapy (MHT) generally considered the mainstay of treatment. However, MHT may be medically contraindicated in some patients and not desired by others. Fezolinetant (Astellas Pharma Inc.), a selective neurokinin-3 inhibitor, is a once daily oral nonhormonal therapy under consideration by the FDA at a 45 mg dose for the treatment of moderate to severe VMS associated with menopause. We compared the clinical and cost effectiveness of fezolinetant and MHT to no pharmacologic treatment and to each other.

Fezolinetant 45 mg (as well as 30 mg) was studied as part of two Phase III randomized controlled trials (RCTs) conducted primarily in the United States (Skylight 1 and 2). At both doses, fezolinetant demonstrated statistically significant improvements in VMS severity and frequency over twelve weeks. However, at the planned 45 mg dose, average improvement in VMS severity compared with placebo achieved a clinically meaningful difference in only one of the trials and the average reduction in VMS frequency failed to achieve a clinically meaningful difference in either trial. There were however higher proportions of treatment responders in the 45 mg trial arms compared to placebo. In terms of safety,

fezolinetant was generally well tolerated, with headache as the most common adverse event and 2-3% experienced elevated liver enzymes. Additionally, a separate trial of the 30 mg dose (Moonlight 1) was reportedly negative, which conflicts with the findings in the Skylight trials. When compared to placebo, MHT achieved clinically significant differences for both VMS frequency and severity.

While 45 mg dosing appears to demonstrate some efficacy, significant uncertainties remain. Negative results in the Moonlight 1 trial raise uncertainties about the consistency of the findings or perhaps the efficacy of fezolinetant in different populations, as Moonlight 1 enrolled patients in Asia. In addition, the short duration of the trials in comparison to the typical duration of VMS also creates uncertainty about long-term efficacy. In terms of safety, fezolinetant was well tolerated and no additional safety concerns were reported in the Phase III safety trials (Skylight 4 and Moonlight 3). However, only limited data from the Phase III RCTs were available for review in this report. In addition, fezolinetant possesses a unique mechanism of action without other in-class data available and liver injury has been documented at higher doses. Given the modest benefit observed in RCTs and uncertainty about long-term benefit and overall safety, we rated the net health benefits of fezolinetant 45 mg compared with no pharmacologic treatment for VMS as “Promising but Inconclusive” (P/I).

In comparing fezolinetant to other interventions (e.g., MHT), there have not been any head-to-head trials with active comparators. In qualitative comparisons of the treatment effects of fezolinetant versus MHT, MHT resulted in greater reductions in both VMS frequency and severity when compared to fezolinetant, but heterogeneity across the trials creates uncertainty about this conclusion. Over the short-term, the safety

Clinical Analyses

and tolerability of fezolinetant and MHT appear comparable. However, longer term use of MHT carries serious increased risks including coronary heart disease, stroke, venous thromboembolism, breast cancer and mortality; this risk may be heightened in

certain subpopulations. In sum, there is considerable uncertainty about the comparative net health benefits of fezolinetant versus MHT, and we rated the evidence for this comparison as “Insufficient” (I).

Economic Analyses

LONG-TERM COST EFFECTIVENESS

We developed a *de novo* decision analytic model to evaluate fezolinetant for the treatment of VMS compared with no pharmacologic treatment. We also conducted an economic evaluation of MHT compared with no pharmacologic treatment. At a placeholder price of \$6,000 annually, fezolinetant exceeds commonly accepted cost-effectiveness benchmarks. Results suggest that fezolinetant would meet these benchmarks and be considered cost-effective if priced at around \$2,000 annually. MHT is widely available as generic medication and is cost-effective.

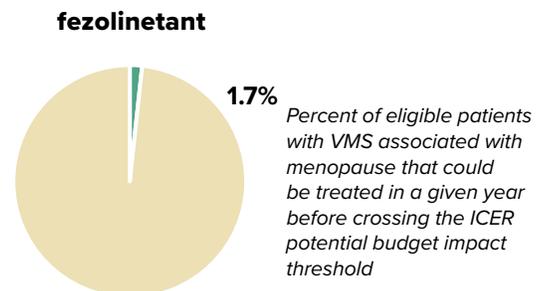
efficacy data are needed. Currently available evidence suggests that it is likely either comparable or may be inferior to MHT in terms of benefits, but this must also be balanced against the known safety profile of MHT and individual patient profiles. The cost-effectiveness of fezolinetant will depend upon its price and whether it is considered an alternative to MHT for all women or whether it will primarily be used by women who cannot or will not take MHT.

Fezolinetant appears promising in the treatment of VMS at the 45 mg dose, but longer-term safety and

Economic Analyses

POTENTIAL BUDGET IMPACT

At fezolinetant’s placeholder price of \$6,000 annually, approximately 1.7% of women could be treated without surpassing the potential budget impact threshold of \$777 million.



Public Meeting Deliberations

VOTING RESULTS

For women seeking relief from vasomotor symptoms associated with menopause:

- A majority of panelists (11-1) found that the evidence is **not adequate** to demonstrate a net health benefit of fezolinetant compared to no pharmacological treatment.
- All panelists (12-0) found that the evidence is **not adequate** to demonstrate a net health benefit of fezolinetant compared to menopausal hormone therapy.

During their deliberations, panel members also weighed the therapy's other potential benefits, disadvantages, and contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- Magnitude of the lifetime impact on individual patients;
- Patients' ability to achieve major goals related to education, work, or family life;
- Society's goal of reducing health inequities.

About ICER

The Institute for Clinical and Economic Review ([ICER](https://www.icer.org)) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through

three core programs: the California Technology Assessment Forum ([CTAF](https://www.ctaf.org)), the Midwest Comparative Effectiveness Public Advisory Council ([Midwest CEPAC](https://www.midwestcepac.org)) and the New England Comparative Effectiveness Public Advisory Council ([New England CEPAC](https://www.newenglandcepac.org)). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

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