PATIENTS RISING NOW

Guide for Commenting on ICER's Draft Evidence Report on Treatments for Menopause Vasomotor Symptoms

On October 11, 2022, ICER released its draft evidence report, "Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause." This document provides a framework for considering what aspects of ICER's review are important to women and their families, and how to consider presenting those perspectives. This guide specifically provides insights about how to read and respond to ICER's draft evidence report, as well as how to request a slot to make comments during ICER's public meeting.

Key Dates

October 11, 2022:	Draft Evidence Report released
November 7, 2022:	Written comments due by 5:00pm ET; deadline to submit request to speak at Public Meeting
December 1, 2022:	Updated Evidence Report released
December 16, 2022:	Public Meeting with ICER's Midwest Comparative Effectiveness Public Advisory Council (CEPAC)
January 23, 2023:	Final Evidence Report and Public Meeting Summary released

Background & How to Participate

The Institute for Clinical and Economic Review (ICER) is a private entity that uses its own analytical process and "value framework" to assess potential new treatments for a variety of diseases. Those assessments often occur before FDA approval, and may result in conclusions that could harm patients by limiting access to new and innovative treatments. You can learn more about ICER here.

There are two primary ways advocates and other stakeholders can give input:

1. **Submit written comments on the draft report, which are due to ICER on November 7th.**
2. **Request a slot to make oral comments during ICER's December 16th meeting.**

Submitting written comments on the draft report

Written comments must be submitted as a Word document via email to publiccomments@icer.org. Comments must be in 12-point Times New Roman font, and no more than 5 pages, not including references or appendices.

The deadline to submit written comments is 5:00pm ET on November 7, 2022.

Requesting a slot to make oral comments

ICER's public meeting on the revised report and discussion by one of its advisory committees will be held virtually on December 16th. You can register for the meeting here. ICER's meetings devote only a short period to public comments by a small number of participants. Oral comments are limited to no more than five minutes per speaker.

To request a slot, send an email to publiccomments@icer.org and include the speaker's name, title, and organization.

The deadline speaking requests is 5:00pm ET on November 7, 2022.

NOTE: Not all requests to make public comments are granted. According to ICER: "We sort through all the requests to make an oral public comment at the meeting. Because we only have a limited time for oral comments at the public meeting, we can only allow a few stakeholders to share their perspective."

What Patients Need to Know about the Quality Adjusted Life Year (QALY)

What is a QALY?

- To understand how ICER's reports can impact patients, it is important to understand the Quality Adjusted Life Year (QALY) concept and how ICER uses it as the basis for much of its analysis and as a justification for its conclusions and recommendations.

- In simple terms, a QALY is a measurement used by health economists to represent one year lived in "perfect health." A year for anyone living in a state of less than "perfect health" is automatically valued lower. Thus, an illness can reduce a hypothetical patient's QALYs – by decreasing their lifespan and/or leaving them with less than perfect health – while an effective treatment would increase them. Entities like ICER use the QALY to determine the "value" of the treatments they review.

Insurance plans – including Medicare and Medicaid – may use those assessments of "value" to make decisions about which treatments are covered and which it will not pay for. This can severely limit patient access to treatments.

- In November 2019, the National Council on Disability, which is an independent federal agency, issued a report "Quality-Adjusted Life Years and the Devaluation of Life with Disability," explaining why patients are not well served by use of the QALY:

  [S]takeholders fear that use of QALYs undervalues vital treatments that extend or improve the lives of people with disabilities. This is because the QALY calculation reduces the value of treatments that do not bring a person back to "perfect health," in the sense of not having a disability and meeting society's definitions of "healthy" and "functioning"; uses simplified assessments of value that do not account for the complexity of patient experience; and does not to take into account clinical expertise on rare disorders that may not have an extensive research literature available for use. Other stakeholders—often from the medical, health economics, and health insurance fields—argue that QALYs provide payers with valuable information on a treatment's potential benefits and costs and aid them in negotiating a reasonable price with the drug (or treatment)'s manufacturers.

  - Patients may also find these reports from the Patient Access and Affordability Project (PAAP) and the Pioneer Institute helpful in understanding how the use of the QALY impacts patients:
    - "ICER uses QALYs to evaluate healthcare," PAAP
    - "Study Urges Caution Before Adopting ICER Reviews to Determine Cost Effectiveness of Treatments," Pioneer Institute
    - "Bad Science: How the use of QALYs creates biased and unreliable outcomes for patients," PAAP
    - "A Better Way: Replacing the QALY with a true, patient-centered quality-of-life measure," PAAP

Key Points to Consider for Stakeholder's Written or Oral Comments

Clinical Effectiveness

- Menopause is part of the normal physiological life course for women as their ovaries decline in function (i.e., produce less hormones), leading to the ending of menses,

and organ-specific and systemic changes from the fluctuation and decline in hormone levels. Menopause may occur naturally, during the aging process, or be the result of surgical removal of the ovaries. On average, menopause starts at about age 45-50, and essentially all women experience vasomotor symptoms (a.k.a., "hot flashes") during menopause. About 40% of women have moderate to severe vasomotor symptoms – generally defined as having more than 7 hot flashes of moderate to severe intensity[1] per day, or more than 50 per week. Vasomotor symptoms typically last about 9 years, but are most bothersome for about 4 years, and can result in trouble sleeping, anxiety, intimacy, and workplace performance.

- There are also some racial and ethnic differences in the likelihood of developing significant vasomotor symptoms, with Black and Native American women more likely to have moderate to severe symptoms compared to white women, while Asian women may have a lower likelihood.

- The current ICER review is focused on medicines for treating the vasomotor symptoms of menopause. While there are many different prescription medicines and other treatments women may use to treat their vasomotor symptoms, ICER's review primarily looks at fezolinetant, which is a potential new oral medicine that impacts the neurotransmitter in the brain involved in the control of body temperature. In its review, ICER compares fezolinetant to existing hormone treatments, (i.e., estrogen with or without progesterone) of different doses and delivered by different routes, i.e., oral and transdermal. ICER's draft report also reviews information about other prescription medicines, including anti-depressants and medicines used to treat neurological pain – specifically gabapentin and pregabalin.

- Fezolinetant is currently undergoing review by the FDA, and a decision is expected from the FDA by February 22, 2023.

- ICER's review found that fezolinetant was effective at reducing the severity and frequency of menopausal vasomotor symptoms, but that hormone therapies may be slightly more effective (ICER found that fezolinetant increased QALYs from a baseline of 16.33 to 16.43, i.e., 0.10 QALYs, while hormone treatments increased QALYs by 0.125). However, because of the variety of studies of hormone therapies that ICER reviewed, there was a range of data for that option. In addition, the studies

[1] Vasomotor symptoms are characterized in ICER's report 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).

of fezolinetant have this far not reported quality of life metrics. There are also potential concerns about the risks of hormone therapy for cancer and cardiovascular conditions – although those risks may be greater for older women (i.e., >age 60) who are less likely to still be experiencing moderate to severe vasomotor symptoms. Conversely, hormone therapies may also improve other symptoms of menopause, such as vaginal dryness, and reduce the risk of fractures.

- Concerning adverse events, ICER's found that for all the treatment options it reviewed, adverse effects were not common or severe (see chart below from draft report). For fezolinetant, the most common adverse event was headache and a dose dependent increase in liver enzymes. However, because the trials were generally short in duration with their follow-up (i.e., at most about 1 year), there are theoretical concerns about longer-term use of any of these medicines. Specific to hormone treatments, ICER's report notes that "Longer term use of [hormone therapy] may result in serious increased risks including coronary heart disease, stroke, venous thromboembolism, breast cancer and mortality, particularly among women ≥60 years old." That is why the report also stated, "We recognize that some women may be at higher risk of harms from [hormone therapy] due to underlying conditions or older age, and in such cases, fezolinetant may be an alternative given its balance of benefits and harms."

Table 3.3. Adverse Events

Drug	Most Common Adverse Event Greater Than Placebo
Fezolinetant	Headache; in larger doses, elevated liver enzymes (ALT and AST)
MHT	Uterine bleeding (more reports of various serious adverse events)
SSRI/SNRI: Desvenlafaxine	Nausea, dry mouth, constipation, fatigue
SSRI/SNRI: Venlafaxine	Dry mouth, fatigue, decreased appetite
SSRI/SNRI: Paroxetine	Nausea, fatigue
SSRI/SNRI: Escitalopram	No adverse events greater than placebo arms
Gabapentin	Dizziness, headache, and somnolence

ALT: alanine transaminase, AST: aspartate aminotransferase, MHT: Menopausal hormone therapy, SNRI: serotonin–norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor

- In addition, while the report's text indicated low disconsolation rates for fezolinetant and hormone treatments compared to placebos, in its economic modeling ICER assumes discontinuation rates of 3.6% for fezolinetant, 6% for hormone treatments, and 1.3% for placebo. It is also noteworthy that in its modeling, ICER assumes that

none of the treatments affected length of life.

- Overall, the report presents a very mixed and muddled picture of the potential treatment options for menopausal vasomotor symptoms, noting significant uncertainties with its own analysis. For example, due to factors like the variety of trials of hormone therapies, ICER was not able to conduct its normal meta-analysis to combine the findings of different trials into a single assessment. Acknowledging that data gap, ICER noted "the definitions of our primary outcomes of [vasomotor symptoms] frequency and severity differed across trials, making cross-trial comparisons more difficult." This is one many aspects of uncertainty that raises questions about the validity and certainty of ICER's conclusions.

- A more qualitative – and patient-focused – aspect of the report is the feedback ICER received from patients and clinicians. Those perspectives clearly expressed the importance of individualization of care and shared decision making for a woman with their care team as a crucial aspect of the treatment of menopause – including vasomotor symptoms.

- Thus, because of the many treatment options for vasomotor symptoms of menopause – and the various other health conditions, risk factors, current medications, and life situations that women in their late 40s and 50s may have – shared decision making to develop an individualized treatment and care plan is critical for women to be able to receive quality care that is appropriate for them.

Recommendation: *Advocates for better treatments for the symptoms of menopause should consider making the following points in their written or oral comments:*

- Menopause is a normal part of aging, but its symptoms – and particularly moderate to severe vasomotor symptoms – can be life altering, interfering with women's ability to function optimally or get adequate sleep for several years. Thus, not only is their quality of life significantly diminished, but so can their work productivity – which can have dramatic implications for women who are in their prime work and earning years.

- Because of the complexity of treating menopausal vasomotor symptoms, women should engage in shared decision making with their clinicians to collaboratively develop individualized treatment plans. And since all existing treatment options have

limitations and different risks, the availability of a new treatment option – such as fezolinetant – would be an important addition to the options available to women.

- Advocates should provide their personal perspectives and insights about menopause and the importance of having more and better treatment options – particularly those that have different mechanisms of actions since different medicines may be more appropriate for people with different underlying medical conditions (e.g., history of cancer or cardiovascular conditions, or after hysterectomy), or life challenges (e.g., work situations where vasomotor symptoms may be particularly problematic).

- Discuss how vasomotor symptoms affects the daily lives and productivity of women going through menopause, i.e., including loss of sleep, anxiety and work productivity.

Cost Effectiveness

- As noted above, ICER's economic modeling and analysis uses the concept of Quality Adjusted Life Years (QALYs) and "utilities" as fundamental components of its economic modeling and analysis. Using QALYs for decisions about payment, coverage, and rationing of care has been widely criticized because QALY calculations assume that people with less than perfect health have diminished quality of life. Therefore, QALYs inherently discriminate against people with chronic conditions and disabilities. For women with menopause who may be in their prime working years, QALY based analyses under-estimate and under-value the impact of vasomotor symptoms on work productivity and earnings.

- In its report, ICER evaluates the clinical effectiveness of different hormone treatments – as well as antidepressants and neurological pain treatments – all of which are available in generic forms. While such options expand choices for patients and clinicians in shared decision making, ICER cost-effectiveness analysis only compares fezolinetant to generic hormone treatments. Together with its "budget impact analysis" (see below) the report sends a clear signal to insurance companies and other payers that, regardless of clinical effectiveness or shared decision making that develops the best care plan for an individual woman, generic medicines are the cheaper option (for the insurance company) and should therefore be given priority in any benefit structure through cost-sharing and prior authorization barriers.

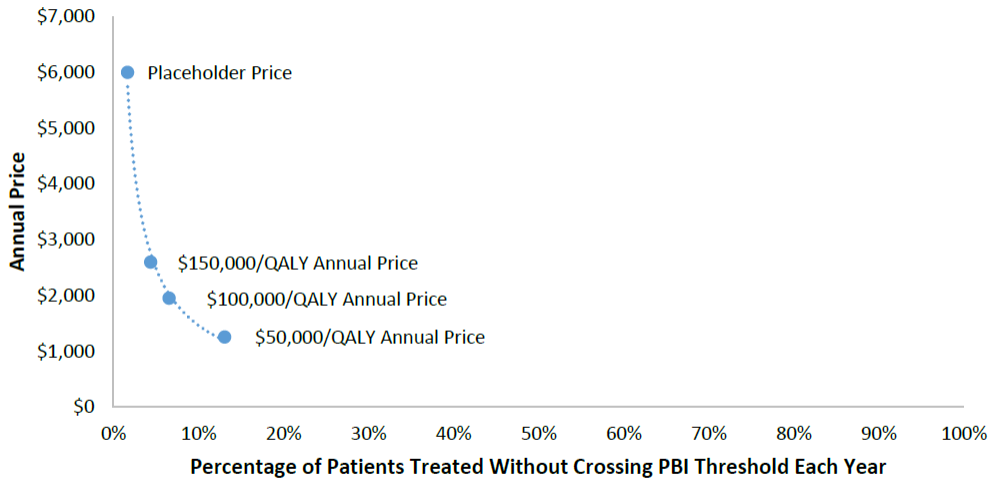
- An additional concern about ICER's economic cost effectiveness modeling is that it does not consider how treatments will improve over time with newer medicines or treatment combinations. That is, while ICER recognizes that fezolinetant provides a treatment option acting through a different mechanism from existing treatments, it downplays the potential benefits of a new option for women with menopause. ICER's report also does not discuss how clinicians and patients could potentially use fezolinetant in combination with other prescription medicines, alternative treatments, and lifestyle modifications as part of an individualized approach to menopausal symptoms.

- As noted above, because of problems in comparing data across different trials of the various treatments, ICER's cost effectiveness analysis does not accurately reflect real world experiences of women. This is also acknowledged in the report: "We acknowledge that women with [vasomotor symptoms] may attempt multiple treatments over the duration of the menopausal transition. The model did not include treatment switching or further attempts at treatment if patients discontinued due to adverse events or lack of efficacy during the first year."

- Another controversial aspect of ICER's reports about potential new treatments is the report's "budget impact" section, which assumes the U.S. healthcare system is a monolithic single payer entity. ICER's budget impact process asserts that in any year, all new medicines should not receive more than a certain amount of money in total – regardless of their benefit to patients. Their spending ceiling is based on the average total spending on medicines in prior years divided by the average number of new treatments the FDA had approved in recent years – which is then increased by U.S. GDP +1.0% per year.

- In ICER's "budget impact analysis," because essentially every woman will go through menopause as they age, and a significant percentage will have moderate to severe vasomotor symptoms (estimated to be about 40%), it is not surprising that ICER found that only a small percentage of women could be treated with fezolinetant (at ICER's estimated price of $6,000/year) before reaching ICER's arbitrary spending cap. Specifically, ICER found that only 1.7% of women could be treated in each year under its budget ceiling. (See graph below showing percentages of menopausal women with moderate or severe vasomotor symptoms that could be treated without exceeding ICER's annual spending cap under various pricing scenarios.)

Figure 7.1. Budgetary Impact of Fezolinetant in Women with VMS Associated with Menopause



PBI: potential budget impact, QALY: quality-adjusted life-year

- This situation illustrates the bizarre nature of ICER's budget analysis since it means any treatment for a common health condition will have "budget impact" problems, likely leading ICER to issues an "alert" in its final report – unless the new treatment will be replacing very expensive current treatments or clinical care.

- In other words, for any health condition with generic medicines available – no matter how minimally effective or how significant the side-effects for the existing treatment – a new medicine faces a huge hurdle in ICER-style analyses to be deemed "high value" because a new treatment will likely be more costly.

Recommendation: *Advocates for better treatments for menopause symptoms should consider making the following points in their written or oral comments:*

- Question ICER's use of QALYs as a fundamental basis for its cost effectiveness evaluation, particularly because of how it discriminates against people with common diseases like menopause that impact people during their prime working years. Similarly, clearly point out that ICER's modeling methodology is based on a large number of assumptions which may not reflect real-life situations.

- While menopause may be seen by some as a common issue of limited concern, it is important to recognize that the symptoms of menopause are life-altering for many women. In addition, vasomotor symptoms of menopause represent another health condition that disproportionately affects women of color. Therefore, obtaining access to new treatment options should be a priority to improve equity in the U.S. healthcare system. Analysis and recommendations using solely an economic, bottom line, cost-effectiveness lens run counter to that objective.

- Insurance companies and other payers should not establish unnecessarily high co-payments, or erect cost-based barriers – such as prior authorization or similar policies. Such access restrictions for menopause treatments are blind to individual patient variability and significantly undermine shared decision making. In other words, a patient's clinical team should not be second-guessed and blocked by insurance company rules or barriers. Advocates should raise those concerns and include their own experiences with not being able to get – or having to overcome significant hurdles to access – medicines recommended by their clinicians because of insurance company rules or processes, such as high-co-payments or prior approval paperwork and reviews.

Conclusions

- Highlight the importance of new treatment options for women with menopause – particularly those with other health conditions and risk factors related to the use of previously available treatment options.

- Summarize and restate your thoughts, and provide overall recommendations for ICER, particularly with regard to the harms ICER's conclusions could cause by limiting access to clinically proven treatments for the vasomotor symptoms of menopause. Such access barriers are of great concern because they could deny treatments for menopausal symptoms that would improve people's mental health, quality of life, and personal and professional productivity.

- Stress how ICER's assessments – based on countless assumptions and uncertainties – shouldn't be used to justify decisions by health insurance companies and government programs to deny payment or create barriers for patients receiving the treatments their physicians recommend.

- Recognize that ICER's economic modeling – which continues to rely on QALYs – perpetuates assumptions and stereotypes about women with significant, life-altering

conditions like menopause. ICER's QALY based approach to assessing various medical treatments thus supports insurance companies and other payers' ability to discriminate against such people by limiting the accessibility and affordability of treatments recommended by their clinicians.