

November 7, 2022

Dr. Steven D. Pearson
President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Dear Dr. Pearson:

The Partnership to Improve Patient Care (PIPC) appreciates the opportunity to provide feedback on ICER's assessment of treatments for vasomotor symptoms associated with menopause. The majority of people going through menopause experience some degree of vasomotor symptoms (VMS) – commonly described as hot flashes or night sweats with about 40% of women experiencing moderate to severe VMS that interferes with their normal life activities.¹ Frequent moderate to severe VMS episodes are associated with interference with sleep, concentration, mood, energy, and sexual activity.² Despite the fact that this impacts a significant portion of the population, there are few treatment options available. Currently the only available treatment is menopausal hormone therapy (MHT), but large groups of women are contraindicated for MHT or are at risk of many of the severe side effects of long-term use of MHT. The Women's Health Initiative (WHI) study³ found that, depending on individual patient characteristics as well as the type and duration of MHT, for some women, the risks of MHT may outweigh the benefits. Given this reality, safe and effective non-hormonal treatment options are an important need. With this in mind, it is important that assessments of treatments to fill this void are conducted responsibly and at a time when full data is available.

ICER's assessment is conducted too early without full data.

In this assessment ICER continues its concerning practice of conducting an assessment before enough evidence is available to do so. ICER conducts traditional cost-utility analysis and much of the data needed to conduct that type of analysis on this treatment is not yet available. PIPC encourages ICER to pause and continue this exercise when critical inputs from trial data to the cost of the medicine are available.

ICER's model is overly simplistic.

ICER builds its model around three states: on-treatment, off-treatment, and death. This assumes that the value is identical for any treatment, or in the case of this model in which there is only one treatment that

¹ Fasero M, Hernández A, Varillas-Delgado D, Coronado PJ. Women with low quality of life by cervantes-short form scale choose menopausal hormone therapy. *European Journal of Obstetrics & Gynecology and Reproductive Biology*. 2020 Sep 1;252:43-9.

² 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 Feb 20;62(2):153-9.

³ Brunner RL, Aragaki A, Barnabei V, Cochrane BB, Gass M, Hendrix S, Lane D, Ockene J, Stefanick M, Woods NF, Yasmineen S. Menopausal symptom experience before and after stopping estrogen therapy in the Women's Health Initiative randomized placebo-controlled trial. *Menopause (New York, NY)*. 2010 Sep;17(5):946.

the value is simply being on the treatment, not the specific benefits received from this treatment. ICER's primary objective of the model is to compare fezolinetant against no treatment. This model is ultimately not able to demonstrate tangible benefit as ICER has very little information about fezolinetant to feed the model.

The patient-reported outcomes tools used to generate utility values are flawed and not representative of the patient experience.

ICER crosswalks MENQOL to EQ5D for the estimation of utility values. PIPC has several concerns about this exercise.

Currently there are no MENQOL scores for fezolinetant as they have not been published yet, so these scores are only applicable to patients on menopausal hormone therapy, and this population is not included in ICER's base case analysis. In addition to this issue, the sample used to develop the tool is not limited to moderate to severe VMS, which is ICER's focus, but includes all stratifications of post-menopausal women.

In addition to this, the crosswalk study ICER uses is questionable as the exercise crosswalks MENQOL to EQ5D-5L. EQ5D-5L has been highlighted as being of questionable validity previously⁴, and has been put 'on hold' by many health technology assessment agencies globally until problems with its method have been addressed.⁵ In addition to this issue, the crosswalk itself had questionable validity, with a goodness of fit of just $R^2=0.347$ – below 0.4 is considered low.

ICER's utility estimates are not in-line with current literature.

ICER's choices of inputs suggest that the improvement of patients on MHT is a gain of 0.017 units of utility. This does not track with QOL studies looking at the difference in QOL of women with and without treatment of MHT. Other studies looking at the health-related quality of life (HrQOL) in menopausal women suggest a more considerable quality of life burden than is implied in the ICER model,^{6,7} with some suggesting that quality of life measured in EQ5D worsens significantly with the number of years of menopause.⁸ ICER's Markov model does not capture this as it ignores length of disease presence.

⁴ Brazier J, Briggs A, Bryan S. EQ-5D-5L: Smaller steps but a major step change?. *Health Economics*. 2018 Jan;27(1):4-6.

⁵ National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L valuation set. 2017. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/eq5d5l_nice_position_statement.pdf.

⁶ Zöllner YF, Acquadro C, Schaefer M. Literature review of instruments to assess health-related quality of life during and after menopause. *Quality of Life Research*. 2005 Mar;14(2):309-27.

⁷ Woods NF, Utian W. Quality of life, menopause, and hormone therapy: an update and recommendations for future research. *Menopause*. 2018 Jul 1;25(7):713-20.

⁸ Liu K, He L, Tang X, Wang J, Li N, Wu Y, Marshall R, Li J, Zhang Z, Liu J, Xu H. Relationship between menopause and health-related quality of life in middle-aged Chinese women: a cross-sectional study. *BMC women's health*. 2014 Dec;14(1):1-9.

One study⁹ concluded that for the base-case analysis, hormone therapy for 15 years resulted in a gain of between 0.11 and 1.49 QALYs depending on age and length of menopause. Set against a lifetime value of 0.10 QALY gain shown in the ICER model, this is as much as a fifteen-fold difference. Similarly, another study,¹⁰ showed that the health state utility values for quality of life with and without treatment showed a delta of between 0.18 and 0.56 depending on the severity of VMS of the patient. Again, this shows the estimate of 0.01 per cycle or a gain of 0.10 QALYs over a lifetime as an extreme underestimate. We would urge ICER to review the existing body of evidence before moving forward and update its models accordingly.

Alternate modeling choices would produce a more accurate model.

A more appropriate way to estimate the impact of fezolinetant with no MENQOL data available would have been to crosswalk directly from rate and severity of VMS, for which there is data on fezolinetant. There is a known and relatively linear correlation between reduction in frequency and severity of VMS and relative changes in quality of life, particularly in moderate and severe patients.¹¹ The use of this crosswalk would overcome the fact that there is no current MENQOL data for fezolinetant and lead to a more accurate model.

Conclusion

ICER lacks key pieces of data to create an accurate model for the treatment's benefit to patients. Where data is missing, ICER makes assumptions and manipulates available data in a way that is unlikely to produce an accurate picture of value to the patient. We continue to be concerned about ICER's reliance on quality-adjusted life years (QALYs) to value treatments, a method that perpetuates not only devaluation of people living with disabilities and chronic conditions but also over-reliance on simplistic modeling and flawed utilities. PIPC urges ICER to pause this assessment until more full data is available and to amend its methodologies more broadly to better reflect the patient experience.

Sincerely,



Tony Coelho
Chairman
Partnership to Improve Patient Care

⁹ Salpeter SR, Buckley NS, Liu H, Salpeter EE. The cost-effectiveness of hormone therapy in younger and older postmenopausal women. *The American journal of medicine*. 2009 Jan 1;122(1):42-52.

¹⁰ Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M. Measuring the impact of menopausal symptoms on quality of life. *British medical journal*. 1993 Oct 2;307(6908):836-40.

¹¹ Pinkerton JV, Abraham L, Bushmakina AG, Cappelleri JC, Komm BS. Relationship between changes in vasomotor symptoms and changes in menopause-specific quality of life and sleep parameters. *Menopause*. 2016 Oct 1;23(10):1060-6.