Fezolinetant for Vasomotor Symptoms Associated with Menopause: Response to Public Comments on Draft Evidence Report

December 1, 2022

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#	Comment	ICER Response
Manufacturers		
Astellas Pharma Inc.		
1.	RECOMMENDATION 1: ICER states fezolinetant 45 mg is the only intervention of interest, and therefore only data for 45 mg should be considered as part of the Evidence Rating: As correctly stated in Table 1.1 of the Draft Evidence Report and in alignment with the FDA New Drug Application and anticipated commercialization of fezolinetant, only the 45 mg dose is a relevant intervention. Other doses of fezolinetant (e.g., 30 mg, 60 mg, 90 mg) have been investigated, but they have not been submitted to the FDA for commercial marketing approval in the United States. The efficacy of fezolinetant 45 mg was consistently demonstrated in the Phase 3 SKYLIGHT 1 and 2 trials in which women with moderate to severe VMS associated with menopause receiving fezolinetant 45 mg experienced a statistically significant reduction in both the frequency and severity of VMS after 4 and 12 weeks' treatment compared to placebo. Improvement in VMS with fezolinetant 45 mg was seen as early as day 1 in the pooled analysis of SKYLIGHT 1 and 2 trials, with consistent improvements for fezolinetant 45 mg vs placebo within week 1 for VMS frequency and as early as week 1 for VMS severity. As such, conclusions regarding the clinical efficacy and safety of fezolinetant in ICER's evaluation should be based solely on the consistent treatment effect observed with the 45 mg dose. A single case of drug-induced liver injury, consisting of asymptomatic ALT and AST elevations in a participant with obesity and nonalcoholic steatohepatitis was documented in a Phase 2 dose-finding study at a dose of fezolinetant 60 mg. That dose is not included in the FDA New Drug Application nor consistent with the anticipated dose and indication for fezolinetant (45 mg). Liver enzyme levels returned to normal after treatment discontinuation in the Phase 2 trial. In the Phase 3 trials, the frequency of elevated liver enzymes was low across groups, and elevations were generally	Our overall conclusions correspond to the 45 mg dosing and this has been clarified in the revised report. However, as is the case with all ICER reviews, we have used all available data and evidence on fezolinetant to inform our certainty about effectiveness and safety of the 45 mg dosing, including data from Phase II and all Phase III trials. To make it clearer that we are focusing on the 45 mg dosing, we have moved our review of available 30 mg efficacy data out of the main report and to the supplement.

	asymptomatic, isolated, transient and resolved on treatment or soon after study drug discontinuation.	
2.	RECOMMENDATION 2: Remediate inappropriate application of minimally clinically important differences (MCIDs) to infer conclusions on clinical meaningfulness of a difference from placebo in mean change from baseline: Page ES2 and Table 3.2 of the Draft Evidence Report draw conclusions regarding the clinical meaningfulness of the difference from placebo in change from baseline in moderate to severe VMS frequency and severity. ICER defines MCIDs for VMS frequency as ≥25 per week or 3.57 per day, VMS severity as ≥0.225, and the Menopause-Specific Quality of Life Questionnaire (MENQoL) score as ≥1.0, using within-patient change MCID thresholds which have been reported in prior studies. These MCID thresholds are applied inappropriately throughout the report by ICER as thresholds for clinically important between-group mean differences. However, within-patient MCID and between-group MCIDs are not interchangeable. The appropriate use of within-patient MCIDs is to classify individual participants as achieving or not achieving the MCID. The proportion of the classified "responders" can then be compared across the treatment groups to provide guidance for interpretation of benefit. In a responder analysis on an individual per-patient level in the pooled Phase 3 SKYLIGHT 1 and SKYLIGHT 2 trials, 55% of women on fezolinetant 45 mg demonstrated clinically meaningful reduction in moderate to severe VMS frequency at week 12 compared with 31% of women on placebo. Clinically meaningful responses were also observed with fezolinetant 45 mg at week 12 on combinations of outcome measures, including VMS frequency, Patient-reported Outcomes Measurement Information System Sleep Disturbance - Short Form 8b (PROMIS SD SF 8b) Total Score, MENQoL Total Score and MENQoL VMS Domain Score.	Some of these data were unavailable at the time of the draft report (e.g., proportion of treatment responders) and will be incorporated into the revised report. However, it is appropriate to evaluate between group differences and to make determinations about the clinical significance of the *average* difference observed between groups. We welcome more detailed data on patient important outcomes that allows us to fully understand within group and between group treatment response.

3.	RECOMMENDATION 3: Newly presented long-term efficacy and safety data should be considered in the clinical evidence evaluation: Data for 1,831 women followed for 52 weeks were recently presented at The North American Menopause Society 2022 Annual Meeting and IMS 18th World Congress on Menopause. These conferences occurred after publication of ICER's Draft Evidence Report. SKYLIGHT 4 was a Phase 3, randomized, placebo controlled, double blind study in 1,831 women investigating the long-term (52-week) efficacy and safety of fezolinetant in women seeking treatment for relief of VMS associated with menopause. Data from SKYLIGHT 4 affirm the safety of fezolinetant 45 mg in terms of endometrial health and bone health. In addition, analysis of the 52-week open-label extension period for SKYLIGHT 1 and 2 found that improvement in VMS frequency and severity observed through week 12 was maintained throughout the 52 week total study period for those receiving fezolinetant 45 mg and the safety profile observed over the duration of the study was consistent with that of the 12 week placebo controlled period. If approved, Astellas anticipates developing additional real-world long-term efficacy and safety data for fezolinetant 45 mg.	Our revised report has been updated to reflect newly available data.
4.	RECOMMENDATION 4: Correctly characterize the full known impact of fezolinetant 45 mg on quality of life: On page 35, ICER states that it is unknown to what degree the observed improvements in VMS frequency and severity translate to improved patient quality of life, citing concern with MENQoL in the Phase 2 trial. As noted in Recommendation 1, only data for fezolinetant 45 mg should be considered as part of the evidence review; ICER should not use Phase 2 30 mg MENQoL data in its final assessment. Analysis of data from the pooled Phase 3 SKYLIGHT 1 and 2 trials show a statistically significant improvement over placebo in quality of life as measured by MENQoL total score (least-squared (LS) mean difference vs placebo of -0.47, 95% CI -0.66, -0.28) at Week 12 (**Error! Reference**	Our revised report has been updated to reflect newly available data.

	source not found.) and individual VMS domain (LS mean difference from placebo of -0.86, 95% CI -1.17, -0.56) at week 12. In addition, pooled data from SKYLIGHT 1 and 2 demonstrated the beneficial effect of fezolinetant 45 mg on three measures of patient-reported sleep disturbance: PROMIS SD SF 8b (LS mean difference from placebo of -2.3, 95% CI -3.3, -1.3), Patient Global Impression of Change (PGI-C) (27.8% much better vs 15.4% on placebo), and Patient Global Impression of Severity (PGI-S) (63.4% reporting mild or no problems vs 55.9% on placebo) at Week 12. Fezolinetant 45 mg was also associated with improvements on Work Productivity and Activity Impairment VMS (WPAI-VMS) measures of absenteeism, presenteeism, activity impairment and overall work productivity loss.	
5.	RECOMMENDATION 5: Further acknowledge the limitations of the simplified approach to the cost-effectiveness analysis: Astellas notes that the structure of the model is very simplistic and does not adequately reflect the co-primary endpoints of reduction in daily mean frequency of moderate to severe VMS and reduction in daily mean severity of moderate to severe VMS from the SKYLIGHT 1 and SKYLIGHT 2 trials. The statistically significant reduction in both frequency and severity of moderate-to-severe VMS with fezolinetant 45 mg in both trials has aligned with improvements in MENQoL total score (as noted in Table 2 above) and may result in reductions in health care resource use. The proposed cost-effectiveness analysis, however, applies the same cost-offsets for all treated patients, regardless of the treatment selected. The model also does not consider the quick onset of action with fezolinetant 45 mg, where an improvement in moderate to severe VMS was observed in the pooled data from SKYLIGHT 1 and 2 beginning on the first day fezolinetant was administered.	The cost-effectiveness model estimates the benefit of treatment from quality-of-life changes associated with frequency and severity of VMS by explicitly modeling changes in EQ-5D-5L scores mapped from the MENQoL as measured in fezolinetant clinical trials. Prior evidence suggests changes in VMS frequency and severity are associated with MENQoL total and VMS sub-scores (Mirkin et al. Menopause 2019). Therefore, model outcomes such as cost per QALY and cost per evLY are a function of changes in both VMS frequency and severity with and without treatment. Moreover, as noted in the prior economic model section of the supplement, the model structure is similar to other analyses such as one conducted by the National Institute for Health and Care Excellence. In reference to reductions in health care resource use, we found no abstracts or publications indicating the impact of fezolinetant on reductions in health care resource use. Therefore, this is not due to the model structure, rather the limited evidence available on cost offsets from treatment specifically with fezolinetant. Please find our description of this limitation in the uncertainty and controversies section of section 4. The final point on quick onset of action is incorrect as the model includes quality of life differences between treatment and no treatment in every

		cycle of the model for all women, including the first cycle or immediate start of treatment.

#	Comment	ICER Response
Patients/Patient Groups		
Black Women's Health Imperative		
1.	Menopausal Hormone Therapy (MHT) and Contraindications in Black Women Suggesting a Need for Non-Hormonal Therapy: Contraindications to MHT include a history of breast cancer, CHD (coronary heart disease), a previous venous thromboembolic (VTE) event or stroke, active liver disease, unexplained vaginal bleeding, high-risk endometrial cancer, or transient ischemic attack. From 2014-2018, African American women were almost 40 percent more likely to die from breast cancer, as compared to non-Hispanic white women. African American women have the highest rates of obesity or being overweight compared to other groups in the United States. About 4 out of 5 African American women are overweight or obese. African American women are twice as likely to have a stroke as compared to non-Hispanic white women. African American are women are 30 percent more likely to die from liver and IBD (intrahepatic bile duct) cancer than non-Hispanic white women. In 2011, the rate of surgical menopause was greater among white women than Black women (17.7 vs 13.2 per 10,000 women). However, by 2014, the racial trends were reversed (24.8 per 10,000 for non-Hispanic white women and 28.4 per 10,000 for non-Hispanic Black women). With FDA approval, outcomes of a non-hormonal therapy for menopause can increase access to treatment for more African American women and potentially reduce the frequency and severity of vasomotor and other menopausal symptoms, improve sleep quality, reduce interference of symptoms with daily life, thus improving quality of life as outlined in ICER's outcomes of interest.	Thank you for the additional information about the risks of MHT in Black women. We have expanded our background to better capture disparate risks of MHT for Black women.
2.	The Black Women's Health Imperative affirms the concept of race and ethnicity as a social and health-impacting construct. The social environment has shifted from a focus on race and ethnicity as predictors, to other determinants such as BMI (body mass index), education, income, and perceived discrimination that may be responsible	We agree, but unfortunately these subgroup data are not available. In general, it would be helpful to have more extensive data collection and there is an opportunity for patient organizations to positively influence manufacturers to expand data collection on social determinants of health.

	for the differences observed between ethnic groups. BWHI recommends ICER investigate how providers collect data about social determinants of health – including patient's employment status, housing status, food insecurity and other life experiences that lead to stress and allostatic loading and offer resourceful information.	
3.	Even though Black women enter menopause earlier, and the symptoms last longer, they are the least likely to leave the (doctor's) office with a prescription for hormone treatment. Some experts suggest this may have to do with the common but erroneous belief that Black people have a higher pain tolerance. Women of color often go to their doctor, and the doctor says, 'Oh, no, you're too young [for menopause]', or they want you to 'grind it out,' and women walk away undiagnosed. Or providers assume patients can't afford hormone replacement therapy or other solutions. Symptoms like "hot flashes" and weight gain can be linked to future heart disease, diabetes, and other serious conditions that are already more prevalent among Black and Latinx women. According to ICER's Draft Evidence Report (October 11, 2022), some patients discussed the lack of recognition of their symptoms by their healthcare providers, causing patients to worry that their symptoms were indicative of the onset of other health conditions. Other patients mentioned that their healthcare providers considered their symptoms as unavoidable parts of menopause and did not offer further information about treatment. The lack of information and recognition of the burden of VMS for menopausal women caused some women to feel disempowered and prevented them from engaging with their healthcare providers on this topic. Instead, in the absence of discussion from their healthcare providers, they sought alternative information sources, such as family members, friends and church members. BWHI recommends ICER include in stakeholder engagement, entities (i.e., local health centers, community-based organizations, faith-based health ministries) that can best collect qualitative data relevant to dynamics between providers and women of color with menopause. Data collection methods may include provider and patient interviews, surveys/questionnaires and focus group discussions.	We appreciate this comment and the partnership in hearing from women firsthand about their experience and have added this context to the patient perspective section of our report.

HealthyWomen		
1.	Our primary concern with ICER's draft evidence report evaluating treatment options for VMS related to menopause is that it hasn't given enough consideration to the real-world effects those symptoms have on women's personal, family and work lives. And similarly, how suboptimal treatment or barriers to access — that could be financial or logistical — are unacceptable. HealthyWomen is very concerned with policies that do not ensure that healthcare treatments are accessible, affordable and safe for all women.	We have expanded the patient perspectives section to reflect impact on personal, family, and work life. Regarding accessible and affordable treatment, when prices are aligned with benefits, patients will have access to needed therapies
2.	To help ICER, its advisory committee and other stakeholders appreciate those real-world aspects of VMS for women as they go about their work and personal lives, HealthyWomen would like to share insights we have gleaned through interviews, surveys and other forms of data collection and synthesis as part of our disseminating actionable information for women.	Thank you and we will include additional information in the patient perspective section.
3.	We highlight those real-world stories because they both illuminate the deep importance of menopause symptoms to actual women, and they contrast with ICER's draft evidence report, which notes that its modeling doesn't reflect real world situations, i.e., "We acknowledge that women with VMS 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."	The goal of the cost-effectiveness analysis is not to model the entire progression of menopausal transition and all therapies available, but rather the goal is to isolate the value and cost-effectiveness of fezolinetant.
4.	Unmet Needs of Women with VMS of Menopause: Clearly, with so many women experiencing VMS and many clinicians currently hesitant to discuss menopause with women, there is a tremendous unmet need for women to understand the changes in their bodies and the options they can access to potentially treat those symptoms. Therefore, having more treatment options — such as fezolinetant — would both provide additional options for women with VMS, as well as prompt clinicians to initiate discussions about menopause and VMS with their patients. Part of the decision-making around the value of new treatment options for VMS are the risks and adverse effects of the current options. ICER's draft evidence report notes that the current standard treatment involves various regimens of hormones, but that those carry significant and uncertain side	We agree that there is an unmet need for non-hormonal treatment for menopause. It is possible that women are less likely to discontinue fezolinetant compared to MHT but as acknowledged, this is the discontinuation across different trials and not head-to-head comparison. Overall, the rates of discontinuation are similar. In addition, the reasons for discontinuation are important (e.g., serious adverse event versus not tolerable). Lastly, we did capture different discontinuation rates in our economic model.

	effects. And most worrisome, ICER's draft report itself notes that menopausal hormone therapy (MHT) is contradicted for many women, i.e., "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 for endometrial cancer, or transient ischemic attack." Therefore, having new treatment options that act through a different physiological pathway is important for women and their clinicians. Specifically, fezolinetant — which acts though a new physiological pathway (i.e., a selective neurokinin-3 (NK3) receptor antagonist) — has been found to have very different side effects than MHT and would likely be an option for women that have contraindications to MHT. While ICER notes that there have not been any head-to-head trials between fezolinetant and MHT, we noted that as part of its modeling ICER concluded that the discontinuation rate for fezolinetant is 3.6%, which was roughly half that of the 6% for MHT. We conclude from ICER's use of that data point that the overall incidence of significant adverse effects for women with VMS is much less for individuals using fezolinetant than MHT.	
5.	Shared Decision-Making Is Key for Women with Vasomotor Symptoms of Menopause: Because of the overall complexity of treating a condition as significant and personal as VMS in women with menopause, we want to emphasize the importance of women working with their care team in a shared decision-making process to determine the treatment course that is best for them. As ICER's draft evidence report states, the North American Menopause Society specifically included in its clinical guidelines that MHT use for VMS "should be determined individually through shared decision-making based on symptom relief, adverse events, and patient preferences."	We agree and ICER's reviews do not attempt to make suggestions for individual patients. We have added text to the Evidence Report citing the NAMS guidelines highlighting shared decision making.
6.	Affordability Is an Important Consideration for Individual Women: We note that the latter parts of ICER's draft evidence report address financial issues. While we appreciate the extent of effort involved in ICER's cost-effectiveness modeling, we strongly believe that the appropriate consideration around financial aspects of healthcare is access and affordability for the individual. Insurance utilization management	ICER's hope is that when prices are aligned with value, access improves – accessibility and affordability are key aspects of ICER's mission.

	processes and formulary restrictions are enormous barriers to access that also impact affordability. Cost-effectiveness modeling may be important, but if affordability for individuals is addressed appropriately in value-based ways, then those other facets of the multi-layered health policy debates will be much easier to solve.	
7.	We also want to address the use of quality adjusted life years (QALYs) to convert real-life consequences of illnesses and health conditions into dollars and cents. As you certainly know, the use of QALYs is not without controversy because it devalues certain people and their health conditions and can lead to rationing in unethical and immoral ways when used in real-world situations. Thus, we are concerned that organizations that would rely on ICER's analysis could use it to create barriers to access for millions of women endeavoring to improve their lives as they seek to obtain better treatment for their VMS of menopause.	ICER wholeheartedly agrees that cost-effectiveness analyses should never be used to discriminate against people with disabilities. However, Americans deserve to know if a treatment improves or harms patients' quality of life. To throw out these measures is to reject patients' lived experience – an experience that has taught us that quality of life should serve as the guide to fair drug pricing and fair patient access
National Menopause Foundation		
1.	During previous conversations with the ICER team about this review process, we stressed some fundamental concerns about the process and its purpose. Primarily, we're concerned that this effectiveness and value assessment and report is conducted before the treatment under review has been FDA-approved and available to all women. Using only clinical trial data to determine the potential effectiveness and value that this innovation brings to the sizeable and diverse audience of women suffering with VMS symptoms during and beyond menopause, compared to treatments already on the market, many of which are now generic, seems premature. If the purpose of the review is to accurately compare pharmacological therapy and non-pharmacological therapy to meet the needs of the incredibly diverse population of menopausal women suffering with VMS symptoms, then the solutions being compared should have some equivalency with regard to the number of women potentially exposed to the treatment and the number of years the treatment has been widely available.	ICER typically assesses treatments near their FDA approval date because that is precisely the moment when an independent analysis of value is most needed to help inform the highly consequential decisions that drugmakers and insurers make around initial pricing and access. Patients and clinicians also need to assess clinical effectiveness at the moment that drugs become available to patients.
2.	While multi-stakeholder organizations, including the National Menopause Foundation, are invited to engage with ICER, offer comments such as these, and participate in the public committee hearing to review the final report, the fundamental purpose and process of the review is set by ICER. It chooses	As mentioned above, ICER reviews treatments near their FDA approval date to help inform stakeholders about the potential value of new and innovative therapies at the time when drugmakers and insurers are making key decisions about launch pricing and access. Additionally, since new

	to review pipeline treatments. This, in and of itself, does not seem to be in the best interest of the patient population that desires more options and formulations of treatments to address their unique needs.	treatments like fezolinetant are available immediately after FDA approval, we find it surprising that a review of fezolinetant would not be considered timely or helpful to inform key stakeholders, including clinicians and patients who will be engaging in the shared decision-making process that is recommended when discussing possible treatments for menopausal VMS.
3.	Given that the findings in this report assign an ICER evidence rating for the overall net health benefits of fezolinetant versus no pharmacologic treatment for VMS of "Promising but Inconclusive" (P/I) and there was considerable uncertainty and insufficient evidence to draw conclusions about the overall net health benefit of fezolinetant vs. MHT, leading to an ICER Evidence Rating of "Insufficient" (I), it seems our concerns about this review process being premature are validated.	As mentioned above, the timing of ICER reviews is meant to provide an independent analysis of value to help inform the highly consequential decisions that drugmakers and insurers make around initial pricing and access. That we found some uncertainties in the evidence and safety around fezolinetant seems important for stakeholders, including payers, clinicians and patients to know as they engage in decision-making about potential therapies to treat menopausal VMS.
4.	An additional concern we raised during this process is that reviewing pipeline therapeutics for long-term cost effectiveness, when they have yet to be FDA-approved, compared to non-pharmacological and pharmacological treatments for VMS symptoms of menopause that have long-term usage data, cost analysis data, and are now often generic, seems disingenuous. Accurately determining the cost effectiveness of any treatment needs long-term, real-world data to evaluate. Instead, as noted in this report, no publicly available list or net price exists for fezolinetant, so ICER used a placeholder price of $6,000 per year for estimates of cost-effectiveness based on analyst market projections and uptake assumptions and then determined this price wasn't cost effective. Review of cost-effectiveness should be done after a treatment has come to market and is in use by its intended audience, not before.	Upon FDA approval, fezolinetant will be on the market and sold regardless of the availability of long-term, real-world evidence to inform pricing of fezolinetant. Given the difficulty of estimating long-term value without long-term data, this would suggest a low launch price until further evidence has been collected. Further, while the cost-effectiveness analysis uses a placeholder price, the report also includes threshold prices to suggest what prices would meet commonly cited cost-effectiveness thresholds.
5.	As noted in the draft report, Section 2: Patient and Caregiver Perspective, healthcare providers interviewed stressed that safe and effective nonhormonal treatment options are an important need for women suffering from VMS symptoms of menopause. And although HRT has been found to have an overall health benefit and is highly cost effective, a recent survey found that 65% of women will not consider using HRTs to treat their menopause symptoms.	We agree. We have added text to the revise report citing the NAMS guidelines highlighting shared decision making.

	From a patient advocacy standpoint, the report's tables 5.1 and 5.2 are critical. These contextual considerations and additional benefits or disadvantages underscore the complexities of addressing the overall health and well-being of menopausal women based on age, ethnicity symptom severability and more. It is imperative that menopausal women have access to all available treatment options, including new non-hormonal options, and that shared-decision between the patient and their healthcare provider is prioritized regarding treatment decisions.	
Society for Women's Health Research		
1.	Choice and Access: Currently, women have extremely limited pharmacologic treatment options for VMS. Those options are even more limited when it comes to non-hormonal therapies. Within its Draft Evidence Report, ICER acknowledges that there are "women who cannot or do not wish to take menopausal hormone therapy (MHT)." Fezolinetant is a first-in-class, once daily, non-hormonal treatment option for menopause-related VMS. As such, fezolinetant can add to the scope of treatment options available for women seeking to treat menopause-related VMS. This consideration will be critical for both ICER and the U.S. Food and Drug Administration (FDA) as they make future decisions related to fezolinetant. Patient values—including individualized treatment options based on a woman's unique circumstances and the ability to contribute to shared decision-making between women and their health care providers—should be acknowledged and valued.	We agree and ICER's reviews do not attempt to make suggestions for individual patients. We have added text to the revised report citing the NAMS guidelines highlighting shared decision making.
2.	Clinical Analysis: Throughout the Draft Evidence Report, ICER recognizes the uncertainty within its analysis. For example, with respect to comparability of outcomes, ICER notes, "While the population characteristics were largely comparable across trials, the definitions of our primary outcomes of VMS frequency and severity differed across trials, making cross-trial comparisons more difficult." Further, ICER shares that there have not been any head-to-head trials with active comparators and that fezolinetant was not compared to selective serotonin reuptake inhibitors (SSRIs)/serotonin–norepinephrine reuptake inhibitors (SNRIs), gabapentin, or pregabalin.	Implications of these and other uncertainties will be raised during the policy roundtable at the public meeting.

	SWHR is concerned that these acknowledgements, while helpful for those reading the report, create uncertainty about the conclusions presented by ICER and leave much room for interpretation for creating coverage and access decisions.	
3.	Allowing Room for Scientific Innovation: Fezolinetant, as a first-in-class, non-hormonal treatment option for menopause-related VMS, represents an important step forward in scientific innovation for menopausal women. Within the Draft Evidence Report for reviewing cost-effectiveness, ICER notes that there is "considerable uncertainty about efficacy and long-term safety" of fezolinetant in the treatment of VMS, though it "appears promising." Science and evidence development is ever-evolving. Fezolinetant is not a systemic hormone treatment; it is a new and unique treatment mechanism that has the potential to evolve and improve over time and, notably, can provide new and beneficial treatment options for menopausal women. As with all scientific innovation, we must look toward the future and the promise of new scientific discoveries. The current Draft Evidence Report does not account for this evolution or the possibility for fezolinetant to be used in combination with other menopause treatments.	ICER welcomes new therapies for unmet needs but it is important to recognize that when new therapies emerge, there is likely to be unknown information about risks and benefits which creates uncertainties. We have attempted to capture both the potential benefits and uncertainties throughout our report.
4.	Finally, SWHR calls attention to a point made in a recent blog post by the Patient Access & Affordability Project on cost effectiveness: "In the draft report, ICER assesses 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. With that approach, ICER sends clear signals to insurance companies and other payers that, regardless of clinical effectiveness or shared decision making to develop the best care plan for an individual patient, generic medicines, as the cheaper option (for the insurance company), should be given priority in any benefit structure through patient cost-sharing and prior authorization barriers." SWHR is concerned that the Draft Evidence Report presented by ICER discounts the potential benefit of fezolinetant by citing the lack of long-term data	ICER's decision to not compare to certain generic therapies is not a signal to payers. Fezolinetant was not compared to some generic medications because of their minimal effectiveness in clinical trials. Our rating of fezolinetant as "Promising but Inconclusive" acknowledges both the potential benefits of fezolinetant but also that there is uncertainty around those benefits due to the lack of complete published data from the pivotal clinical trials.

	available and remarks that the cost-effectiveness of the drug "will depend upon its price and whether it is considered an alternative treatment to MHT for all women or whether it will primarily be used by women who cannot or will not take MHT."	
5.	SWHR encourages the Institute to keep in mind that additional choice is a valuable outcome for a significant portion of this population. Further, fezolinetant has the potential to meet the direct needs of women who are not going to take other treatments; if other treatments on the market were sufficient to meet women's needs, the need for fezolinetant would be moot.	We agree.

#	Comment	ICER Response
Other		
Paul Langley (College of Pharmacy, University of Minnesota)[this grid includes only feedback relevant to the current review, please refer to public comment folio on our website for all comments provided]		
1.	Let me turn to your crosswalking from the Menopause-Specific Quality of Life Questionnaire (MENQOL) to the ordinal numbers that comprise the EQ-5D-%L. Remember: the object for Rasch measurement for non-physical attributes is for a single attribute interval score. Multiattribute disease specific instruments have to be disaggregated and Rasch assessment applied. The MENQOL was introduced in 1996 as a tool to assess health-related quality of life in the immediate post-menopausal period. The MENQOL is a multi-domain instrument. Rather than consider latent traits or attributes that may be relevant to the response of post-menopausal patients to therapy interventions, including the question of whether the needs of these patients are being met, the MENQOL proposes to assess the quality of life in terms of 29 items in a Likert-format capturing patient-reported symptoms experienced in the preceding month: vasomotor (items 1–3), psychosocial (items 4–10), physical (items 11–26), and sexual (items 27–29). Items pertaining to a specific symptom are rated as present or not present. If the symptom is present it is scored on a zero (not bothersome) to six (extremely bothersome) scale. Non-endorsement of an item is score I; endorsement a 2. Each domain is scored separately, with subject responses converted to a composite mean range 1 to 8 (endorsement score plus Likert integer value). The overall questionnaire score is a mean of the domain items.	The cost-effectiveness model estimates the benefit of treatment from quality-of-life changes associated with frequency and severity of VMS by explicitly modeling changes in EQ-5D-5L scores mapped from the MENQoL as measured in fezolinetant clinical trials. Prior evidence suggests changes in VMS frequency and severity are associated with MENQoL total and VMS sub-scores (Mirkin et al. Menopause 2019). Therefore, model outcomes such as cost per QALY and cost per evLY are a function of changes in both VMS frequency and severity specific to fezolinetant and no treatment, among the other treatments in the model.
2.	In the ICER report, the crosswalk to translate MENQOL scores to create the EQ-5D-5L score is: EQ-5D-5L = 0.992 – 0.042 *MENQOL The fundamental error associated with this ordinary-least squares regression model, although it should be noted that the fit is poor with a reported R^2 = 0.347 and root mean squared error of 0.093, is the fact that both the EQ-5D-5L and MENMQOL are just numbers or ordinal scores; they both fail to meet Rasch measurement standards. This means that crosswalking using a regression model is disallowed; no attempt was made to demonstrate that the scores were interval or ratio, just the assumption, which is incorrect, that the MENQOL score is a continuous	See above comment.

	variable; in fact, it has neither ratio not interval properties. The MENQOL is just a summation of scores which have no discernible properties to support mean values by domain and average of domain means	
Partnership to Improve Patient Care		
1.	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 typically assesses treatments near their FDA approval date because that is precisely the moment when an independent analysis of value is most needed to help inform the highly consequential decisions that drugmakers and insurers make around initial pricing and access. Additionally, since new therapies such as fezolinetant are immediately available for use upon FDA approval, we find it surprising that a review of fezolinetant would not be considered timely or useful by clinicians and patients who will be considering whether fezolinetant is an appropriate treatment for VMS.
2.	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 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.	See above comment. The information on the MENQoL from fezolinetant was masked in the draft report to adhere to ICERs academic-in-confidence policy. As the manufacturer of fezolinetant has publicly released previous academic-in-confidence data, there will be a greater level of transparency in our revised Evidence Report.
3.	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 previously, and has been put 'on hold' by many health technology assessment agencies globally until problems with its method have been	The information on the MENQoL from fezolinetant was masked in the draft report to adhere to ICERs academic-in-confidence policy. Please find the MENQoL data on fezolinetant in the revised Evidence Report and Final Evidence Report. We acknowledge the limitations of crosswalking/mapping from the MENQoL to the EQ-5D-5L. According to the fezolinetant phase III protocol located on clinicaltrials.gov, EQ-5D-5L scores were collected by the manufacturer and we requested the data but did not receive this information. We also welcome direct utility valuations of VMS severity and frequency from the manufacturer and other stakeholder groups.

	addressed. In addition to this issue, the crosswalk itself had questionable validity, with a goodness of fit of just R2=0.347 – below 0.4 is considered low.	
4.	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, with some suggesting that quality of life measured in EQ5D worsens significantly with the number of years of menopause. ICER's Markov model does not capture this as it ignores length of disease presence. One study 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, 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.	While we relied on the MENQoL mapping/crosswalk exercise, the baseline utility value for those not treated with symptoms was 0.811. This baseline utility estimate is very similar but slightly lower than one of the studies referenced in this public response (e.g., baseline age-adjusted utility score for ages 50-64 was 0.82 in Salpeter et al. Am J Med 2009). Further this baseline estimate is in the range of other studies that elicited EQ-5D scores among women with moderate to severe VMS (e.g., Whiteley et al. Menopause 2013). As we noted in the draft report, caution should be exercised when comparing these results to prior studies that may include more or fewer complications associated with MHT in addition to differences in duration of treatment as these key inputs would alter both cost changes and quality of life changes. In reference to quality-of-life gains on treatment, estimates in the cost-effectiveness analysis were derived directly from clinical trials of the therapies evaluated. Therefore, any differences in quality of life from treatment are a reflection of the performance of those therapies on quality-of-life outcomes in well controlled studies.
5.	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. 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.	The information on the MENQoL from fezolinetant was masked in the draft report to adhere to ICERs academic-in-confidence policy. We did include the MENQoL data and used the referenced crosswalk algorithm to generate EQ-5D-5L scores. We also note a prior study suggesting changes in VMS frequency and severity are associated with MENQoL total and VMS sub-scores (Mirkin et al. Menopause 2019). That said, we welcome direct utility valuations of VMS severity and frequency from the manufacturer and other stakeholder groups. Thank you for confirming our approach produces an accurate understanding of the cost-effectiveness of fezolinetant and other treatments assessed in the draft report.