November 7, 2022

Submitted electronically to: publiccomments@icer.org
Institute for Clinical and Economic Review (ICER)

Astellas appreciates the opportunity to provide comment on ICER's October 11, 2022 Draft Evidence Report for the assessment of fezolinetant for moderate to severe vasomotor symptoms (VMS) associated with menopause, characterized by hot flashes (also called hot flushes) and/or night sweats. Following guidelines from professional organizations such as the American College of Obstetricians and Gynecologists (ACOG), North American Menopause Society (NAMS), and Endocrine Society, we encourage ICER to take a patient-centered approach that stresses the importance of shared decision-making for women with VMS associated with menopause and considers risks/benefits, goals, and individual preference. Astellas is committed to turning innovative science into effective medical solutions that bring value to patients. We are focused on helping to address the unmet medical needs of women with moderate to severe VMS associated with menopause as part of our broader vision to turn innovative science into value for patients.

We have reviewed the draft report and wish to submit the following recommendations to improve the accuracy of ICER's conclusions.

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[1] 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.[3,4,5] 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.[6] 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.

Table 1. Key Trial Results for Fezolinetant 45 mg: Mean change from baseline at Week 12

Trial Name/Author	Intervention	Arm Size	Moderate to Severe VMS Frequency	Moderate to Severe VMS Severity
			Difference from Placebo: Mean change (SE)	Difference from Placebo: Mean change (SE)
SKYLIGHT 1 Lederman et al. 2022[3]	Fezolinetant 45 mg	174	-2.55 (0.43) p<0.001	-0.20 (0.08); p=0.007
	Placebo	175	REF	REF
SKYLIGHT 2 Johnson et al. 2021, Johnson et al. 2022[4,5]	Fezolinetant 45 mg	167	-2.53 (0.55), p<0.001	-0.29 (0.08); p<0.001
	Placebo	167	REF	REF

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.[7] 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 asymptomatic, isolated, transient and resolved on treatment or soon after study drug discontinuation.[3,4,5,8]

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.[9,10,11] 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.[12] 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.[9,10]

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.[13] 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.[13]

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.[8,14] Data from SKYLIGHT 4 affirm the safety of fezolinetant 45 mg in terms of endometrial health and bone health.[14] 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. [5,15]

If approved, Astellas anticipates developing additional real-world long-term efficacy and safety data for fezolinetant 45 mg.

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 (Table 2) and individual VMS domain (LS mean difference from placebo of -0.86, 95% CI -1.17, -0.56) at week 12.[16]

Table 2. Pooled Analysis of MENQoL Total Score Results from the SKYLIGHT 1 and SKYLIGHT 2 studies[16]

Trial Name/Author	Intervention	LS Mean change from baseline (95% CI)	LS mean difference from Placebo (95% CI)
Week 4	Fezolinetant 45 mg	-1.27 (-1.39, -1.14)	-0.57 (-0.75, -0.39)
	Placebo	-0.70 (-0.83, -0.57)	REF
Week 12	Fezolinetant 45 mg	-1.31 (-1.45, -1.18)	-0.47 (-0.66, -0.28)
	Placebo	-0.84 (-0.98, -0.70)	REF

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.[17] 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.[16]

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.[6]

In closing, we appreciate the opportunity to provide these recommendations for revising the Draft Evidence Report. We reiterate ICER should recognize in its value assessment the importance of a patient-centered approach and shared decision making for women with VMS associated with menopause. Astellas is dedicated to improving the health of patients through the provision of innovative and reliable pharmaceutical products.

Sincerely,

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BLACK WOMEN'S HEALTH IMPERATIVE

The Black Women's Health Imperative's Response & Recommendations to ICER's Draft Evidence Report, Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause: Effectiveness and Value (October 11, 2022)

Submitted Electronically To: Kelsey Gosselin kgosselin@icer.org

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The Black Women's Health Imperative (BWHI) is appreciative of the opportunity to comment on the Institute for Clinical and Economic Review's (ICER) Draft Evidence Report, *Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause: Effectiveness and Value*, and acknowledges ICER's aim 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 judgements about the clinical and economic value of the interventions".[1] We at BWHI believe the potential effects of fezolinetant will help meet society's goal of reducing health inequities in access to treatment for menopause.

Established originally as the National Black Women's Health Project in 1983, the Black Women's Health Imperative is the first and only national non-profit organization created for and by Black women dedicated to improving the health and wellness of our nation's 21 million Black women and girls -- physically, emotionally, and financially. Our core mission is advancing health equity, and reproductive and social justice, for Black women across the lifespan through policy, advocacy, education, research, and leadership development.

Menopause and Black Women

Much of what we know about how Black women experience menopause comes from the largest ongoing study of women and menopause conducted by the Study of Women's Health Across the Nation (SWAN), a multi-site longitudinal, epidemiologic study designed to examine the health of women during their middle years.[2]

Menopause presents differently in Black women. The average age of menopause in the U.S. is 51. SWAN findings reveal that Black women tend to begin menopause about nine months earlier than white women. Other SWAN findings show that Black and Hispanic women endure "hot flashes" for several years longer than other racial and ethnic groups (10 and 9 years, respectively, versus 6.5 years for non-Hispanic white women), and Black women experience irregular bleeding for longer periods of time than white women. Black women are also three times more likely to experience premature menopause (menopause before age 40), sometimes caused by smoking or autoimmune conditions such as lupus or rheumatoid arthritis – compared with White women,

leading to a 40 percent higher risk of developing coronary disease (which is listed as a contraindication in ICER's Draft Background and Scope, June 1, 2022) over their lifetime.[3]

More than 1 million women in the United States experience menopause each year. Still, little is known about the health effects of this natural biological occurrence. National Institutes on Aging-funded researchers are working to better understand what causes menopause symptoms and how women from diverse racial and ethnic backgrounds can benefit from that scientific knowledge to live healthier lives — before, during, and after menopause.[4]

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.[1] From 2014-2018, African American women were almost 40 percent more likely to die from breast cancer, as compared to non-Hispanic white women.[5] 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.[6] African American women are twice as likely to have a stroke as compared to non-Hispanic white women.[7] African American are women are 30 percent more likely to die from liver and IBD (intrahepatic bile duct) cancer than non-Hispanic white women.[8]

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).[9] 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.[1]

Black Women's Health Imperative's Suggestions: Fezolinetant as a Potential Societal Benefit for Reducing Health Disparities

Access To Care: Intersectionality of Structural Racism, Stress and Menopause

A 2022 SWAN study published in *Women's Midlife Health* proposes that some of the disparities that exist between white women and women of color in perimenopause and menopause are likely attributable to structural racism in the U.S. Although this link has yet to be definitively proven, allostatic load can lead to long-lasting health ramifications, including an earlier, more challenging menopause. Allostatic load refers to the wear and tear from lifetime and ongoing stressors that Black women disproportionately face compared with white women. Systemic racism, including poor access to healthcare, toxic work environments, unsafe neighborhoods, socioeconomic

challenges and more, can weather the body, over-taxing various hormonal and biological processes and fueling chronic inflammation.[3]

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 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.[10]

Provider Relations and Misconceptions

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.[3]

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.[11]

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.*

Thank you for the opportunity to offer comments on *ICER's Draft Evidence Report: Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause: Effectiveness and Value.* The Black Women's Health Imperative looks forward to ongoing engagement on this relevant trailblazing topic.

Sincerely,

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November 7, 2022

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HealthyWomen is pleased to have the opportunity to provide written comments to the Institute for Clinical and Economic Review (ICER) concerning its draft evidence report about vasomotor symptoms (VMS) associated with menopause. As the nation's leading nonprofit women's health information source dedicated to educating and empowering women ages 35-64 to make informed decisions about their healthcare, we want to convey the perspectives of our millions of women readers and constituents to ICER and its advisors about this critical women's health issue.

As you know, menopause is a natural process of aging[i], and even though you consulted with a few patients and other stakeholders in developing your draft evidence report, we feel a perspective is missing. We want to share our knowledge from our extensive engagement with real women and practicing clinicians about their experiences living with and treating VMS of menopause.

Real World Implications of VMS of Menopause for Women

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.

As an organization that engages with women and their clinicians to provide educational and informational material about important health conditions, HealthyWomen has conducted educational programs and published many articles about menopause and VMS, in particular. While we greatly appreciate the importance of clinical research to inform both regulatory and clinical decisions, the actual practice of medicine still encompasses a large measure of "art" involving individualization of care based upon every woman's healthcare goals, needs, and situation. That is why shared decision-making between a woman and her clinicians is so critically important.

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.

VMS during menopause is common and significantly affects women's quality of life. For example, the North American Menopause Society estimates that about three out of four women develop hot flashes around the time of menopause.[ii] However, we've noted that only about one in four women find hot flashes affecting their quality of life so much that they turn to their healthcare providers (HCPs) to seek relief. There are various reasons why women do not seek treatment, often having to do with options available and understanding them. This lack of treatment, however, can have lasting negative implications for a woman's health.[iii]

In addition, VMS may actually put women at risk for other conditions, including cardiovascular disease[iv, v] and osteoporosis. While this is still an area of active research, a summary of research based upon the seminal SWAN study stated that "VMS have traditionally been conceptualized as an important quality of life issue during the menopausal transition, and they have generally not been assumed to have specific implications for physical health. However, emerging research from SWAN and other studies has begun to call this assumption into question."[vi]

The problems women have getting treatment for their menopause symptoms is not isolated. A review by AARP noted that "A Yale University review of insurance claims from more than 500,000 women in various stages of menopause states that while 60 percent of women with significant menopausal symptoms seek medical attention, **nearly three-quarters of them are left untreated**."[vii] (emphasis added)

VMS from menopause can dramatically affect a woman's work life and productivity. For example, in December 2021, we published a story that included part of an interview with Nancy Belcher, Ph.D., about how her VMS during an interview cost her a job opportunity: "Five minutes in, I felt my cheeks flushing and the sweat coming. My hot flashes were bad, and I had sweat dripping down my face." Belcher's interviewer, whom she says was a woman about five years her senior, silently got up and handed her a box of tissues. "I was soaked, the interview was a bust, and I never heard back from her."[viii]

The importance of VMS of menopause for women's work lives shouldn't be underestimated or undervalued. Not only are 21.1% of all workers in the U.S. women between the ages of 45 and 64 (32.25 million),[ix] but a 2019 survey that found that 59% of female workers ages 45 to 55 said symptoms of menopause made it more difficult to concentrate, increased their stress levels and made them less patient at work. One third of surveyed women reported taking menopause-related sick leave, yet only 25% felt comfortable telling their supervisors the reasons for their absence.[x] Similarly, a Harvard Business Review article chronicled the challenges women with significant menopause symptoms face in the workplace, and it concluded that "Menopause is one of the strongest and most discriminatory taboos still existing in the workplace. The mental and physical symptoms and their negative effects on women's productivity are needlessly exacerbated by poor policies and persistent, outdated, gender- and age-related assumptions."[xi]

And just as vasomotor symptoms affect women's work lives, without appropriate treatment, they also can alter their personal lives. Such aspects of health conditions are uniquely captured in HealthyWomen's signature series, "Real Women, Real Stories." In a recent September article, Gabriella Espinosa discussed her experience with menopause: "When I started to enter perimenopause 13 years ago, I'd never even heard the word. Menopause was never mentioned let alone *discussed* in my family or among my friends. When I was in my 40s, busy raising kids, running my business, enjoying a nice family life and a happy marriage, my sex drive suddenly vanished. It was like somebody turned off a light switch. I had no idea why, and I didn't have the language to communicate what I was experiencing to my husband or to anyone, least of all a healthcare provider. I asked myself: Is this aging? Is something wrong with me? Am I broken? Is my sex life over?"[xii] Gabriella's story illuminates the challenges faced by many women as they try to talk with their clinicians and family about menopause. Fortunately, Gabriella learned how to talk with people about her menopause so she could get treatments for the symptoms and be open with her husband.

And Gabriella's story is not unique. Nina Coslov went down a similar path, which led her to co-founding Women Living Better, an organization dedicated to improving women's understanding of the path to menopause through research and education, and then becoming the lead author on "Symptom Experience During the Late Reproductive Stage and the Menopausal Transition: Observations From the Women Living Better survey."[xiii]

In two other similar stories we've published, we heard from Michelle Pursel who experienced sleepless nights because of sweating. She said that "I usually get three hours [of sleep] because of the sweating. The heat starts at the bottom of my feet and moves all the way up my body. No matter how cold I make the bedroom, I'm burning up and pouring sweat."[xiv] And from Stacia Crawford, who had a similar story of battling night sweats and hot flashes for years. "Some nights I was unable to sleep because I would go from burning up to freezing in a matter of minutes," noting that she's often changing her sheets several times a week. She also added. "I also keep a change of clothes in my [car] trunk because sometimes my shirts get so wet it's uncomfortable and embarrassing."[xv]

Overall, there is a tremendous need to bring discussions of menopause symptoms out of the dark. That is clearly a multi-faceted job, but having more treatment options will prompt clinicians to be more open to starting those discussions since they will feel better equipped to help women with their VMS. Those discussions are particularly important since VMS can mimic other conditions. Women shouldn't face barriers to discussing their symptoms – menopausal or otherwise – with their clinicians.[xvi] Unfortunately, there are still significant challenges for women discussing menopause with their clinicians. As a result we published "How To Talk to Your Healthcare Provider About Menopause" in January 2022.[xvii]

Fortunately, there are clinicians who are capable of talking with their patients about menopause. One of those is Dr. Octavia Cannon, who provided her insights about vasomotor and other symptoms of menopause — including racial differences — in a HealthyWomen interview."[xviii]

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."[xix]

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 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."[xx]

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.[xxi] 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.

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."[xxii]

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 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.

Fortunately, the Affordable Care Act placed annual limits on out-of-pocket (OOP) spending for essentially all people with insurance. However, we are also seeing more insurance plans that have very restricted networks and formularies, which means that any costs from those out of network providers and off-formulary treatments may not count toward those OOP limits. And this is happening despite insurance premiums rising significantly, e.g., federal employees' premiums are expected to increase 8.7% in 2023[xxiii] and ACA marketplace plans will be increasing by up to 15%.[xxiv]

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.

Conclusions

HealthyWomen believes time has long since passed for there to be new treatment options to address such a common occurrence for midlife women as VMS during menopause. For those seeking treatment — and even those currently under treatment — having an option of another non-hormonal therapy that acts through a unique physiological pathway is evidenced-based, and clinically sound could be life-changing.

HealthyWomen also strongly believes that the choice of treatments for women should be based on individual circumstances and their shared decision-making with their clinicians. Similarly, affordability and accessibility to treatment options is essential since merely having a new treatment approved by the FDA does not help women with her VMS.

Thank you for the opportunity to comment on this important matter.

Sincerely,

Martha Nolan, J.D.
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1 November 2022

My dear Dr Pearson

PUBLIC COMMENT: FEZOLINETANT FOR MODERATE TO SEVERE VASOMOTOR SYMPTOMS ASSOCIATED WITH MENOPAUSE: EFFECTIVENESS AND VALUE

I refer to your recently released draft evidence report for **Fezolinetant for Moderate to Severe Vasomotor Symptoms associated with Menopause** [1]

As you will no doubt recall, you are aware of my concerns that the ICER reference case framework for value assessment, the creation of assumption driven imaginary claims fails to meet the standards of normal science [2]. That is, given the standards for credibility of claims, empirical evaluation and replication, that distinguish science from pseudoscience, you persist in creating these cost-effectiveness models when it is quite clear that they have no validity. Your reports for modeled claims, many of which are produced by expert academic groups, lack credibility in the claims made for the value of products; they cannot be evaluated empirically nor can the claims be replicated. Your models also violate the fundamental axioms of Rasch or modern measurement theory in confusing ordinal scales with interval and ratio scales. While you might view these reports and the application of lifetime incremental cost-per-QALY calculations and the application of cost-per-QALY thresholds as the state of the art in health technology assessment, the problem is that the entire exercise is essentially a waste of time. This has been detailed in a recent publication in F1000Research which has addressed the manifest deficiencies in the CHEERS 22 guidance for constructing imaginary worlds, described as the ISPOR/ICER meme or belief system for inventing (non-evaluable by design) value claims for cost-effectiveness [3] [4]. Your effort to assess effectiveness and value for fezolinetant is by the standards of normal science and Rasch measurement, an analytical dead-end.

In order for you and your academic consultants to actually come to terms with Rasch measurement, which you will deny by retreating to your strange claim that health economists have confidence that EQ-5D-3L/35L utilities are ratio measures in disguise might I, to emphasize the importance of the Rasch model, quote in full the abstract from a 1989 commentary by Wright and Linacre:

> *Quantitative observations are based on counting observed events or levels of performance. Meaningful measurement is based on the arithmetical properties of interval scales. The Rasch measurement model provides the necessary and sufficient means to transform ordinal counts into linear measures. Imperfect unidimensionality and other threats to linear measurement can be assessed by means of fit statistics. The Rasch model is being successfully applied to rating scales* [5].

To which we might add that interval scales are only relevant if we are measuring a single attribute; confounding different attributes into a single score is hazardous and unacceptable. If an entity of interest has a number of attributes of interest, then they must be assessed individually. Questionnaire items must, therefore, relate to a single underlying attribute; otherwise, our scores are unintelligible. Consider construct validity: the key here is order where test items conform to expected ability to succeed and item difficulty. Items must be judged on their 'reasonable' fit within the test construct to support claims for unidimensionality and the contribution of items that construct interval scales; with the potential to rewrite or discard misfitting items. This is in contrast to data fishing where we trawl through data or items to find a subset that give the 'best' statistical results; this is not measurement or even an acceptable basis for hypothesis testing but it characterizes crosswalking or mapping between instruments.

If you and your academic consultants are still unconvinced by what is now over 60 years since the application of simultaneous conjoint measurement was introduced by Luce and Tukey, and independently by Rasch [6] [7] suggest you consider two textbooks in measurement for non-physical attributes on the social sciences (e.g., quality of life) by Bond at al and Andrich and Marais respectively [8] [9].

May I also point out that the valuation of bundles of health states with the tine trade off technique also fails Rasch measurement. Not only are you bringing together possible attributes into a 'score;' but the fact that these are subjective (qualitative) assessments or expressed opinions means you are dealing with numbers. While you might assume these are on a ratio (and not even an interval) scale, that is a false assumption. An assessment is not a measure (with interval properties). I suggest you read the textbooks referenced [8] [9].

Presenting responses on a visual analogue scale (VAS), constrained for example to 0 (e.g., death) and 1 (e.g., perfect health) is nothing more than a string of numbers or raw score responses which is subjectively assigned by the respondent when asked to 'value' a bundle of symptoms with each symptom defined by response level. A VAS is an integral part of the EQ-5D-3L/5L instruments. As such, it is meaningless; it is just an ordinal ranking of numbers. The differences between the subjective valuations are unknown although placing numbers on a scale which has equal intervals gives the misleading impression that, with a constrained zero, we have not just a false interval scale but a false ratio scale.

It is absurd to try to produce interval or ratio measures from subjective values. This means that utility or preference scales rest on an insecure foundation; the time trade-off (TTO) and standard gamble (SG) responses are only numbers on an ordinal scale. They can be ranked but the distance is subjective. This means they can only support nonparametric statistics; not classical statistical

operations involving addition and subtraction, which require an interval scale. This failure to appreciate the Rasch concept of a measure is obvious from the early days of developing response numbers for the TTO to support the creation of regression based preference algorithm estimates with TTO weights; and to further support the quality adjusted life year (QALY) in assumption driven lifetime simulation models [10]. Despite the attention given to the TTO, if respondents argue for the relevance of negative scores that are worse than death; an arbitrary zero point, the result is still a series of ordered numbers.

The TTO has come in for considerable criticism, a recent evaluation concluding that it is has *too many flaws to adequately quantify a subjective phenomenon such as health* [11]. Among these, assuming it is meaningful to attempt quantification, the authors point to its failure to recognize the requirements of fundamental measurement as it applies in the physical sciences where the focus is on single, unidimensional attributes and invariance in application across measurement contexts. Unfortunately, while reference is made to simultaneous conjoint measurement, the Luce and Tukey paper [16], there is no attempt to point to the unique status of Rasch measurement to capture patient-centric measures with required interval properties.

The mistake made, and this applies to what we describe as integer valued Likert scales, is that to plot subjective estimates on a number line with equal intervals does not mean that the subjective distances on the number line can be manipulated as if they were real numbers on an interval scale; commonly seen where core value sets are proposed for specific disease areas [12]. Asking a sample of respondents to value the same health state description and take the resulting distribution as a basis for assigning mean values and standard deviations is simply absurd; the data points are all ordinal subjective guesses. All we can claim from an ordinal scale are medians and percentile ranges.

Apart from its failure as a score, the TTO has been subject to a range of criticisms; the net result is a recommendation for it to be abandoned [15]. If it is abandoned this puts the generic multiattribute generic scores in a quandary; how can the preferences, which are now disallowed, support QALYs? The answer is straightforward: the QALY is an impossible mathematical construct as are any non-evaluable cost-effectiveness claims built on the impossible QALY.

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 [13]. 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.

Failure to appreciate the limitation of fundamental measurement means that these scores are meaningless. Apart from the adding in of the bothersome/non-bothersome score, the Likert integers in their traditional scale data summation is based on two a priori assumptions: all Likert items are of equal difficulty and that the thresholds between steps are of equal distance or equal value [14]. In other words, the MENQOL scoring fails what has been described as the Rasch or modern measurement quality control test. Judged by the Likert items separately scored, the scores on those items are, in the absence of application of the Rasch Rating Scale Model for polytomous Likert-type data to assess measurement properties have to be regarded as ordinal and not interval or ratio data [15] [16] The addition of the bothersome/non-bothersome score creates additional confusion, possibly best described as an 'adjusted' ordinal scale. It is worth noting that one recent study of the MENQOL claimed it had, through Rasch analysis, acceptable psychometric properties with factor analysis indicating six domains [17]. Unfortunately, Rasch analysis was misapplied to the overall MEMQOL ordinal score, rather than considering the Likert-properties of the instrument and the application of statistics for assessment using the Rasch Rating Scale Model: (i) Overall instrument and item functioning (reliability, fit); (ii) Unidimensionality of underlying construct; (iii) Local independence of items; (iv) Category and threshold functioning; (v) Differential item functioning; and (vi) Person and item alignment [18].

What is doubly unfortunate is that if the authors of this instrument had been aware of the standards for Rasch measurement, known since the 1960s with the application of conjoint simultaneous measurement in instrument development, together with the limitation of fundamental measurement, an acceptable instrument for the quality of life in menopause might have emerged. As it is the instrument is used widely by those, presumably, who are unaware of the measurement requirements of polytomous scales. This is in contrast to instruments focused on needs in quality of life have been developed to meet Rasch standards [19]. Despite its undoubted popularity and increasing use over the past 25 or more years, the fact is that as a polytomous multi-domain instrument, no one questioned its measurement properties (or their absence) including authors of systematic reviews [20] .

In the ICER report, the crosswalk to translate MENQOL scores to create the EQ-5D-5L score is:

$$\text{EQ-5D-5L} = 0.992 - 0.042 * \text{MENQOL}$$

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 [21]. 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 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,

Once the inadvisability of believing that crosswalking between ordinal scores is allowed, is admitted, the entire ICER modelling exercise collapses. The contrived EQ-5D-5L preferences, and consequent creation of mathematically impossible QALYS and assumption driven imaginary comparative cost-per-QALY claims is impossible. There is, presumably, a limit on how far-fetched assumptions can be to support a cost-per-QALY model that fails accepted standards. Unfortunately, given ICER's commitment to cost-per-QALY assumption driven simulations, there has to be a source, however whimsical, of multiattribute generic preferences (preferably the EQ-5D-3L/5L) to justify the model claims. In this case the choice was unwise, irrespective of the model framework not meeting the standards of normal science.

The MENQOL is not the only instrument that has been developed to assess the symptom burden and quality of life in perimenopausal and post-menopausal patients (the so-called climacteric syndrome) [22]. It is not been the intent here to review these instruments, although the assessment of the MENQOL has made clear the assessment standards that should apply. Among the other instruments that have been developed are: (i) the Menopause Symptoms Treatment Satisfaction Question (MS-TSQ); (ii) the Kupperman Index (KI) [23]; (iii) the Menopause Rating Scale (MRS) [24] ; and (iv) the Greene Climacteric Scale [25] . All are polytomous Likert-based instruments with multiple integer scored response options. None have been assessed for Rasch measurement properties (e.g., Rasch Rating Scale Model) for an approximation to an interval score, with the various authors and commentators assuming that the ordinal integer-based summation scale has properties to support classical statistical analysis, which is incorrect as shown by the Tao et al study [26].

The obvious conclusion is that this modeling should be abandoned and the evidence report withdrawn. But we know this will not happen. You will simply reiterate your belief that numbers are measures and that we can with compete confidence crosswalk between multiattribute ordinal scales as the accepted standard in health technology assessment.

Yours sincerely

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Submitted electronically to publiccomments@icer.org.

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Re: Draft Evidence Report: "Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause: Effectiveness and Value"

Dear Dr. Pearson:

The National Menopause Foundation appreciates the opportunity to comment on the Institute for Clinical and Economic Review (ICER) Draft Evidence Report on the effectiveness and value of fezolinetant for the vasomotor symptoms (VMS) associated with menopause.

The National Menopause Foundation was founded in 2019 to be a trusted and relatable resource to raise awareness and understanding of menopause through education, activism, and community building. It was established by and for women to create an informed community where women can learn, exchange information, find support, and be inspired as they approach and journey through Menopause. We intend to destigmatizes Menopause by increasing the public awareness, knowledge, and positive perception of this phase in women's lives.

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.

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 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.

As noted in the draft report, 80 percent of women undergoing menopause experience vasomotor symptoms (VMS). Menopause-associated VMS have a profound negative impact on key health, quality of life, work productivity, and economic outcomes.[iiiiiiivv]

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.**

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.**

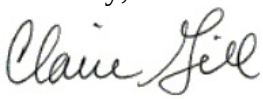
As noted in the draft report, Section 2: Patient and Caregiver Perspective, healthcare providers interviewed stressed that safe and effective nonhormonal treatment options are an important need for women suffering from VMS symptoms of menopause. And although HRT has been found to have an overall health benefit and is highly cost effective, a recent survey[vi] **found that 65% of women will not consider using HRTs to treat their menopause symptoms.**

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.

Thank you for the opportunity to share these comments. NMF looks forward to further discussion of this report during the December 16, 2022, public committee review. If you have any questions regarding these comments or would like further information, please feel free to contact me at cgill@nationalmenopausefoundation.org.

Sincerely,



Claire Gill
Founder
National Menopause Foundation

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[i] Thurston RC. Vasomotor symptoms: natural history, physiology, and links with cardiovascular health. Climacteric. 2018;21(2):96-199.

[ii] Thurston RC. In: Crandall CJ, ed. Menopause Practice: A Clinician's Guide. 6th ed. Pepper Park, OH: North American Society; 2019:43-55.

[iii] Crandall CJ, Aragaki A, Cauley JA, et al. Associations of menopausal vasomotor symptoms with fracture incidence. J Clin Endocrinol Metab. 2015;100(2):524-534.

[iv] Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: a comprehensive review. Associations of menopausal vasomotor symptoms with fracture incidence. Health Qual Life Outcomes. 2005;3:47. doi.org/10.1186/1477-7572-3-47.

[v] Sarrel P, Portman D, Lefebvre P. et al. Incremental direct and indirect costs of untreated vasomotor symptoms. Menopause. 2015;22(3):260-266.

[vi] https://cdn.shopify.com/s/files/1/0011/8590/6751/files/Bonafide_State_of_Menopause.pdf?v=1624280664

PIPC Partnership to Improve Patient Care

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) study[3] 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, Yasmeen 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 previously[4], 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 R2=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 study[9] 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 is 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, Bushmakin 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.

Society for Women's Health Research

November 7, 2022

Submitted electronically to publiccomments@icer.org.

Steven D. Pearson, MD, MSc, President
Institute for Clinical and Economic Review
14 Beacon Street, Suite 800
Boston, MA 02108

Re: Draft Evidence Report on Treatment for Vasomotor Symptoms Associated with Menopause

Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide input to the Institute for Clinical and Economic Review (ICER) on its Draft Evidence Report assessing the comparative clinical effectiveness and value of fezolinetant for the treatment of vasomotor symptoms (VMS) associated with menopause. Given that approximately 1.3 million women transition into menopause each year, at an average age of 51 in the United States[1] and that VMS, or hot flashes and night sweats, can affect quality of life, SWHR recognizes the need for additional treatments and interventions to assist women during this natural life stage.

SWHR, a more than 30-year-old national nonprofit organization based in Washington, D.C., is widely recognized as a thought leader in promoting research on biological sex differences in disease and eliminating imbalances in care for women through our science, policy, and education work. This includes work in menopause. Specifically, SWHR has developed tools and resources to promote the health and wellness of women transitioning to menopause, including the release of a menopause toolkit in 2022, and continues to encourage thought leaders and policymakers to take a lifespan approach when it comes to the health of women—considering how life stages such as puberty, pregnancy, and menopause could affect other aspects of a woman's health.

In its comments on the Draft Scoping Document, SWHR called attention to the burden of VMS symptoms in menopausal women—including that the majority of women (73%) are not treating their menopause symptoms;[2] women of different races and ethnicities have different experiences with VMS, with African American women reporting the greatest duration[3] and highest incidence of hot flashes; [4] and that VMS have been strongly associated with reduced health-related quality

[1] Takahashi TA, Johnson KM. Menopause. Med Clin North Am. 2015 May;99(3):521–534.
[2] State of Menopause Survey. Bonafide. https://hellobonafide.com/pages/state-of-menopause Accessed 16 June 2022.
[3] Avis NE, Crawford SL, Greendale G, et al. Duration of Menopausal Vasomotor Symptoms Over the Menopause Transition. JAMA Intern Med. 2015 Apr;175(4):531-539
[4] Green R, Santoro N. Menopausal Symptoms and Ethnicity: The Study of Women's Health Across the Nation. Womens Health (Lond). 2009 Mar;5(2):127-133

of life, affecting outcomes including sleep, mood, and cognitive function—and commented on the outcomes of interest, scope of comparative value analyses, and evaluation of direct and indirect costs.

Through this particular comment opportunity, SWHR will share a few key points for ICER's consideration. At the heart of these comments are that access and affordability, the ability to engage in shared decision-making, and scientific innovation should be not just acknowledged, but valued and reflected within ICER's final conclusions.

Key Considerations in Response to the ICER Draft Evidence Report on Fezolinetant

SWHR raises the following points in response to the Draft Evidence Report:

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)."

It is essential that women be provided with as much choice as possible when it comes to establishing a treatment plan, especially when considering that menopause is a highly individualized life stage, with no one woman's symptoms and symptom severity being the same. ICER's *Patient and Caregiver Perspectives* section within the Draft Evidence Report reiterates this point, citing clinicians' comments that "depending on the individual patient characteristics as well as the type (e.g., route of administration, dose, combination hormones) and duration of MHT, for some women the risks of MHT may outweigh the benefits." For example, as shared in an article from *Human Reproduction Update*, "Postmenopausal woman are commonly treated with hormone replacement therapy (HRT) to treat climacteric symptoms and prevent bone loss; however, HRT may reactivate endometriosis and stimulate malignant transformation in women with a history of endometriosis."[5] Thus, safe and effective non-hormonal treatment options are an important need."

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.

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

[5] Gemmell LC, Webster KE, Kirtley S, Vincent K, Zondervan KT, Becker CM. The management of menopause in women with a history of endometriosis: a systematic review. Hum Reprod Update. 2017 Jul 1;23(4):481-500. doi: 10.1093/humupd/dmx011. PMID: 28498913; PMCID: PMC5850813.

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.

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.

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.

Finally, SWHR calls attention to a point made in a recent blog post by the Patient Access & Affordability Project on cost effectiveness:

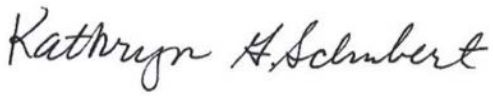
> "In the draft report, ICER assesses the clinical effectiveness of different hormone treatments – as well as antidepressants and neurological pain treatments – all of which are available in generic forms. While such options expand choices for patients and clinicians in shared decision making, ICER cost-effectiveness 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 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."

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.

Thank you for your consideration of the above comments. SWHR looks forward to engaging with ICER during this assessment and on other future topics affecting women's health. If you have questions or need any additional information that would be helpful to inform ICER's value assessment, please contact me at kathryn@swhr.org or Lindsey Horan, Chief Advocacy Officer, at lindsey@swhr.org.

Sincerely,



Kathryn G. Schubert, MPP, CAE
President and CEO
Society for Women's Health Research