Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause: Final Policy Recommendations

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Policy Recommendations

Introduction

The following policy recommendations reflect the main themes and points made during the Policy Roundtable discussion at the December 16, 2022 Midwest Comparative Effectiveness Public Advisory Council (CEPAC) public meeting on the use of fezolinetant for the treatment of moderate to severe vasomotor symptoms. At the meeting, ICER presented the findings of its revised report on these treatments and the Midwest CEPAC voting council deliberated on key questions related to their comparative clinical effectiveness, potential other benefits and contextual considerations, and long-term value for money at current prices. Following the votes, ICER convened a Policy Roundtable of two patients, two clinical experts, two payers, and one representative from the pharmaceutical manufacturer to discuss how best to apply the evidence and votes to real-world practice and policy. The discussion reflected multiple perspectives and opinions, and therefore, none of the statements below should be taken as a consensus view held by all participants.

A recording of the conversation can be accessed here and a recording of the voting portion of the meeting can be accessed here. More information on Policy Roundtable participants, including conflict of interest disclosures, can be found in the appendix of this document. ICER's report on these treatments, which includes the same policy recommendations, can be found here.

The roundtable discussion was facilitated by Dr. Steven Pearson, MD, MSc, President of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

All Stakeholders

Recommendation 1

All stakeholders have a responsibility and an important role to play in ensuring that women have access to effective new treatment options for symptoms of menopause and that such options are introduced in a way that encourages shared medical decision making and equitable access to treatment options.

Having additional safe and effective nonhormonal options for treatment of vasomotor symptoms (VMS) of menopause is an unmet health care need. Many women who have VMS do not receive treatment because symptoms are underrecognized or undertreated by health care providers. In addition, while clinical experts and patients highlighted that menopausal hormone therapy (MHT) was an effective and affordable option, many patients cannot (e.g., history of breast cancer) or will not take MHT because of concerns about side effects. Therefore, all parties have a role to play in

ensuring appropriate access to new treatment options for menopause after they are approved by the FDA.

To address these concerns:

Manufacturers should take the following actions:

- Align pricing of fezolinetant (if approved by the FDA) and other emerging treatment options with their cost effectiveness and health benefit price benchmarks.
- Advertise fezolinetant and other newly available treatment options in a way that does not exaggerate the risks of MHT.

Payers should take the following actions:

- Ensure that coverage policies enable equitable access to treatment options and allow women who cannot or will not take MHT access to nonhormonal options.

Clinical societies and patient organizations should take the following actions:

- Develop and disseminate educational materials and create guidelines to not only enable informed shared decision-making, but to increase awareness of menopause and its treatments.

Payers

Recommendation 1

Given that there are other treatment options available for many women, payers can use evidence to create coverage criteria for fezolinetant that reflect whether the manufacturer prices the drug in fair alignment with its benefits for patients.

If fezolinetant is approved by the FDA, it will have a place in therapy. However, given the significant uncertainties around its longer-term safety and effectiveness, and the fact that patients have other treatment options available, it is not unreasonable for payers to consider the pricing for fezolinetant in how they design coverage criteria. If the drug is priced in reasonable alignment with its benefits to patients, payers should utilize less restrictive coverage language and should ensure that fezolinetant is tiered on the lowest relevant tier – preferred brand. However, should the manufacturer set a price above reasonable cost-effectiveness levels, it is reasonable for payers to use more restrictive prior authorization as a component of coverage (e.g., restriction to women with a contraindication or intolerance to MHT and/or severe symptoms). Regardless, any prior authorization criteria should be based on clinical evidence, and payers should consider input from clinical experts and patient organizations. The process for prior authorization should also be clear,

accessible, efficient, and timely for providers. Perspectives on specific elements of cost sharing and coverage criteria within insurance coverage policy are discussed below. Relevant Fair Access Design Criteria set out in ICER's previous work are included.

Cost Sharing

- Patient cost sharing should be based on the net price to the plan sponsor, not the unnegotiated list price.
- If all drugs in a drug class are priced so that they represent a fair value, it remains reasonable for payers to use preferential formulary placement with tiered cost sharing to help achieve lower overall costs.

Coverage Criteria: General

ICER has previously described general criteria for fair coverage policies that should be considered as cornerstones of any drug coverage policy: https://icer.org/wp-content/uploads/2020/11/Cornerstones-of-Fair-Drug-Coverage-_-September-28-2020-corrections-1-5-21.pdf

Drug-Specific Coverage Criteria: Fezolinetant

Coverage Criteria

- **Age:** Age criteria are likely to follow the FDA label. The clinical trials of fezolinetant enrolled women ages 40-65, but clinical experts suggested a specific age range is not required to narrow treatment to a clinically appropriate population and that this should be at the discretion of the treating provider. However, clinicians did express concern about younger menopausal women (e.g., premature ovarian insufficiency) receiving fezolinetant when they would benefit from the broader effects of MHT. Clinical experts also thought fezolinetant could be appropriate for women older than those enrolled in the clinical trials who had persistent VMS due to menopause.
- **Clinical eligibility**: The FDA label may be very broad, to include treatment of VMS due to menopause for all patients, or it may follow the eligibility language of the pivotal trials to craft a narrower label focused on treatment of patients with "moderate to severe VMS." Given the uncertainty in long-term outcomes and the fact that this is a first-in-class therapeutic, it is not unreasonable for payers to consider whether to use the specific trial eligibility criteria to define a threshold for frequency/severity of VMS that merits coverage. Trial eligibility required "a minimum of 7-8 moderate-to-severe hot flashes per day or 50-60 per week." "Moderate" hot flashes were defined as a sensation of heat with sweating. The advantages of applying the pivotal trial criteria to insurance coverage is that it could target

coverage to patients who stand the most to benefit from treatment. However, clinical experts did not believe that it was appropriate to use strict thresholds based on the frequency of VMS given that patients may have fewer very severe episodes that still have a substantial impact on quality of life. If payers choose to apply a threshold for frequency/severity to coverage, they should be primed to reconsider their approach as more data become available on the longer-term effectiveness and safety of the drug.

- **Step Therapy:** Given that many patients may benefit from readily available, effective, and low cost MHT, clinical experts agreed that it would be reasonable for payers to require prescriber attestation that patients are not appropriate candidates for MHT prior to prescribing fezolinetant. Such an attestation would serve to document that there is a contraindication or intolerance to MHT or unwillingness to take MHT after a shared medical decision-making discussion has occurred. Clinical experts also felt that using such an attestation was reasonable and sufficient. Given the dearth of evidence demonstrating long-term safety and effectiveness, it is not recommended that payers require step therapy with SNRI/SSRIs or gabapentinoids as a condition of coverage for fezolinetant.

- **Exclusion criteria**: Pre-existing liver disease will likely be considered a contra-indication based on side effect concerns and clinical trial eligibility criteria.

- **Duration of coverage and renewal criteria**: Although menopausal symptoms may wax and wane before eventually ending, clinical experts strongly advised against any requirements for 'drug holidays' to evaluate whether symptoms have resolved. Clinical experts stated that best practice was to continually re-evaluate treatment effectiveness and need for treatment at regular medical visits. Experts thought that initial coverage for a period of three - six months would be sufficient to determine treatment effectiveness and whether therapy should continue, but that attestation for continuation of therapy should not be required.

- **Provider restrictions**: Although an argument could be made to limit prescribing to experts in women's health given the importance of full shared decision-making regarding the relative risks and benefits of treatment options for VMS, the vast majority of women receive their care from generalist physicians, and any attempt to narrow the providers able to prescribe would also disproportionately worsen access to care for patients with more limited economic resources or who do not have easy access to specialists. Provider restrictions for fezolinetant would therefore not be a reasonable element of insurance coverage.

Manufacturers

Recommendation 1

Manufacturers should seek to set prices that will foster affordability and access for all patients by aligning prices with the patient-centered therapeutic value of their treatments. In the setting of new nonhormonal treatments for menopause, there is considerable optimism about emerging therapies, but there is also considerable uncertainty about longer-term safety and effectiveness especially in the case of first-in-class medications. Manufacturer pricing should reflect these considerations in their initial pricing.

Manufacturers should price novel treatments in accordance with the demonstrated benefits to patients. In settings of substantial uncertainty, initial pricing should err on the side of being more affordable. This would allow more patients access, generating additional data on the real-world effectiveness of novel treatments that could be used in future assessment updates. With accumulation of evidence of substantial patient benefit, manufacturers should be allowed to increase pricing in accordance with benefit.

Recommendation 2

Manufacturers should be transparent with the results of all clinical trials, especially those that include null findings.

There is an ethical imperative for manufacturers to make public the results of all trials. In the case of fezolinetant, a press release was issued citing negative findings for the top-line results of the Asia-based Moonlight 1 trial, but more detailed results have not been released. Although this study evaluated a different dose than is ultimately being reviewed for US approval, it is important to examine the entirety of evidence for novel therapeutics. Multiple stakeholders expressed concern about the lack of peer reviewed evidence or results published in trial registries prior to potential FDA-approval of this drug with a new mechanism of action.

Recommendation 3

Manufacturers should engage in responsible direct-to-consumer advertising by refraining from approaches that could unreasonably heighten concerns about the risks of hormonal treatment.

Manufacturers should accept responsibility not to drive up concerns of well-established competitor treatments. Thus, manufacturer advertising (both direct-to-consumer and to clinicians) should highlight new treatment options without emphasizing the potential harms of MHT since clinical experts believe that most women can benefit from the broader effects of MHT.

Recommendation 4

Manufacturers should support the development of improved measures of menopause severity and quality of life outcomes that are meaningful to patients.

Clinical experts identified the lack of standard definitions of severity and frequency in menopause and limitations of traditionally applied minimum clinically important differences. We also heard from patients and advocacy groups that endpoints used in clinical trials do not always measure what is most important to patients. Both clinicians and patients cited the Menopause-Specific Quality of Life (MENQOL) Questionnaire as an instrument that is likely outdated. Moreover, the MENQOL cannot be readily translated into utility measures and incorporated into cost effectiveness analyses. Patient organizations along with researchers can also assist in collaborating with manufacturers and regulators to define a core set of outcomes for use in future clinical trials.

Clinicians and Clinical Societies

Recommendation 1

Clinical societies should update treatment guidelines for patients seeking treatment for symptoms of menopause to reflect current treatment options in a form that is easy to interpret and use by clinicians, patients, and payers.

Clinical societies should be prepared to rapidly update and disseminate guidance on new therapies. Payers are very sensitive to guidance coming from specialty societies, particularly as it concerns early new treatments such as fezolinetant. Societies such as the North American Menopause Society and their clinical guidelines are influential in payers' coverage decisions. Policy roundtable participants highlighted that guidelines should not only provide information on options to be used by clinicians and patients for shared decision making, but also offer pragmatic advice about how to select specific therapies for specific subgroups (e.g., women over the age of 60).

Patient Organizations

Recommendation 1

Patient organizations have a vital role to play to promote objective descriptions of the risks and benefits of new therapies in order to support shared decision-making for every patient. In addition, patient groups have a powerful voice and should apply it to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system.

Patient organizations should endeavor to educate patients about the potential risks and benefits of different treatment options including hormonal and nonhormonal therapy. Patient organizations should work with other stakeholders to develop and disseminate evidence-based, balanced

materials that are accessible to all patients, including those with low health literacy. Patient groups should also accept responsibility to publicly promote access and fair pricing of new therapies.

Researchers/Regulators

Recommendation 1

Funding agencies such as the National Institutes of Health should ensure adequate funding for women's health, including the study of menopause.

Clinical experts emphasized that there is a still a lack of understanding of the underlying mechanisms that drive vasomotor dysfunction in menopause and that this contributes to a lack of effective treatment options. In addition, more research is needed to understand MHT outside of historical studies such as the Women's Health Initiative, particularly among younger women, across racial groups, and with newer formulations of MHT. Head-to-head trials of different options for VMS are needed and clinical trials must ensure that they enroll diverse subpopulations to adequately reflect the population undergoing menopause. Research efforts should also incorporate new measures of quality of life and improved assessments of minimum clinically important differences.

Appendix

Appendix Tables 1 through 3 contain conflict of interest (COI) disclosures for all participants at the December 16, 2022 Public meeting of the Midwest CEPAC.

Appendix Table 1. ICER Staff and Consultants and COI Disclosures

ICER Staff and Consultants	
Francesca Beaudoin, MD, PhD, MS,* Senior Medical Advisor, ICER	**Grace Lin, MD,*** Medical Director for Health Technology Assessment, ICER
Shahariar Mohammed Fahim, PhD,* Research Lead, Evidence Synthesis	**Brett McQueen, PhD,*** Assistant Professor, Department of Clinical Pharmacy, University of Colorado
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Yasmine Kayali, BA,* Program Coordinator, ICER	

*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 2. Midwest CEPAC Panel Member Participants and COI Disclosures

Participating Members of CEPAC	
Alan Balch, PhD* CEO, National Patient Advocate Foundation	**Bradley Martin, PharmD, PhD*** Professor, University of Arkansas for Medical Sciences
Bijan Borah, PhD* Professor of Health Services Research, Mayo Clinic College of Medicine and Science	**Timothy McBride, PhD*** Professor, Washington University in St. Louis, and Co-Director, Center for Health Economics and Policy
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*No conflicts of interest to disclose, defined as individual health care stock ownership (including anyone in the member's household) in any company with a product under study, including comparators, at the meeting in excess of $10,000 during the previous year, or any health care consultancy income from the manufacturer of the product or comparators being evaluated.

Appendix Table 3. Policy Roundtable Participants and COI Disclosures

Policy Roundtable Participant	Conflict of Interest
Shontelle Dodson, PharmD, Executive Vice President, Head Medical Affairs, Astellas Pharma Inc.	Dr. Dodson is a full-time employee of Astellas Pharma Inc.
Stephanie Faubion, MD, MBA, Director, Center for Women's Health, Mayo Clinic. Medical Director, North American Medical Society	No conflicts to disclose
Claire Gill, Founder, National Menopause Foundation (NMF)	The NMF received program-specific support totaling less than 25% from Astellas Pharma, Inc.
Deb Grady, MD, MPH, Professor of Medicine, UCSF	No conflicts to disclose
Paula Green-Smith, MA, Chief Training Officer, Black Women's Health Imperative (BWHI)	Black Women's Health Imperative receives funding from Hologic Inc., Gilead Sciences, and Myovant-Pfizer.
Michelle Rogers, PharmD, BCPS, Director, Clinical Pharmacy, IPD Analytics	Dr. Rogers is a full-time employee of IPD Analytics
John Watkins, PharmD, MPH, BCPS, Residency Program Director, Premera Blue Cross, and Affiliate Professor, University of Washington	Dr. Watkins is a half-time employee of Premera Blue Cross.