Fezolinetant for Moderate to Severe Vasomotor Symptoms Associated with Menopause

Draft Background and Scope

June 1, 2022

Background

Eighty percent of women undergoing menopause experience vasomotor symptoms (VMS). VMS, characterized by hot flashes and night sweats, are thought to be brought on by decreased estrogen levels and increased neurokinin B (NKB) activity acting on the hypothalamus, which regulates body temperature.[1-3] The change in hypothalamic thermoregulation increases blood flow to the skin, resulting in the VMS. Hot flashes typically develop as a sudden onset of heat in the upper chest and face which spreads throughout the body and that lasts two to four minutes. Hot flashes are often accompanied by profuse sweating and, when this occurs at night (night sweats), can cause sleep disruption. Additionally, the combination of vasodilation and sweating can rapidly lower body temperature and cause shivering.

The frequency of VMS varies from one per day to one per hour. Most women who have them experience several per day. The intensity of VMS can be classified as mild (sensation of heat without sweating), moderate (sensation of heat with sweating but able to continue activity), or severe (sensation of heat with sweating, causing cessation of activity). The median duration of vasomotor symptoms is 7.4 years.[4,5] Risk factors for developing vasomotor symptoms include obesity, smoking, reduced physical activity, high follicle-stimulating hormone (FSH) levels, and mutations in the tachykinin receptor 3 gene, which encodes the NKB receptor.[6,7] Further, Black women typically have the longest duration of symptoms compared to white women while Hispanic and Chinese women typically have the shortest duration of symptoms.[8] Vasomotor symptoms are estimated to increase direct healthcare costs by $1,346 per person per year compared to women without symptoms, and increase indirect economic costs due to missed work by another $770 per person per year.[9]

While many women describe their VMS symptoms as severe, only 20 to 30 percent of women seek medical treatment. Treatment options vary based on symptom severity. Women with mild VMS symptoms are recommended to try behavioral approaches, such as lowering ambient temperature, dressing in layers of clothing, and avoiding physical and emotional triggers (e.g., spicy foods and stressful situations). For women with moderate to severe VMS and no contraindications,

menopausal hormone therapy (MHT), consisting of estrogen and a progestin or progesterone (for women with an intact uterus) or estrogen alone (for women who have undergone a hysterectomy) is recommended as first-line therapy. Contraindications to MHT include a history of breast cancer, 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.[10] Additionally, women with high cardiovascular disease risk or moderate to high risk for breast cancer are recommended to try nonhormonal therapies.

Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) are commonly recommended nonhormonal treatment classes. While paroxetine is the only antidepressant with an FDA-approved indication for vasomotor symptoms, other SSRI and SNRIs can also be used for treatment. Further, paroxetine is not recommended for women on tamoxifen, a selective estrogen receptor modulator used to treat breast cancer. Anti-epileptics (gabapentin and pregabalin) are often recommended for women with sleep disturbances as they can aid sleep.

Many women try complementary and alternative therapies to manage vasomotor symptoms. Common therapies include cognitive behavioral therapy, yoga, exercise, acupuncture, isoflavones, phytoestrogens, and black cohosh. However, the evidence for the effectiveness of these treatments is, at best, inconclusive.

Fezolinetant (Astellas Pharma Inc.) is a once daily oral non-hormonal therapy being investigated for the treatment of moderate to severe VMS associated with menopause. It acts by regulating neuronal activity in the hypothalamus thereby affecting temperature regulation. If approved, it would be the first selective neurokinin-3 (NK3) receptor antagonist available in the US. Astellas is anticipating submission of a New Drug Application to the FDA in 2022.

Stakeholder Input

This draft scoping document was developed with input from diverse stakeholders, including patient representatives, clinicians, researchers, and the manufacturer of the agent of focus in this review. This document incorporates feedback gathered during preliminary calls with stakeholders and open input submissions from the public. A revised scoping document will be posted following a three-week public comment period. ICER looks forward to continued engagement with stakeholders throughout its review and encourages comments to refine our understanding of the clinical effectiveness and value of preventive treatments.

The majority of women experience VMS associated with menopause, though for many, symptoms are mild and may or may not require treatment. However, the FDA guidance for industry on clinical evaluation is to include women with 7 to 8 moderate-to-severe hot flashes per day.[11] Researchers advised that this is a small percentage of the women who experience VMS, so clinical trial results may not necessarily be applicable women whose symptoms are not as severe. Research experts

also highlighted the progression of symptoms. For most women, symptoms tend to attenuate over time and most women stop taking treatments after months to a few years. However, some women have hot flashes lasting for up to 10-20 years. Additionally, while the prevalence of VMS varies by sociodemographic factors, that variation in prevalence decreases during the menopausal transition since most women experience symptoms.

In our discussion with clinicians, we heard that the heightened risk of cardiovascular disease with estrogen and progestin seen in the Women's Health Initiative (WHI) study may not generalize to treatment of VMS given that treatment tends to start at a younger age and be of shorter duration than in the WHI.[12]

Report Aim

This project will evaluate the health and economic outcomes of fezolinetant for vasomotor symptoms associated with menopause. The ICER value framework includes both quantitative and qualitative comparisons across treatments 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 judgments about the clinical and economic value of the interventions.

Scope of Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see ICER's grey literature policy).

All relevant evidence will be synthesized qualitatively or quantitatively. Wherever possible, we will seek out head-to-head studies of the interventions and comparators of interest. Data permitting, we will also consider combined use of direct and indirect evidence in network meta-analyses of selected outcomes. Full details regarding the literature search, screening strategy, data extraction, and evidence synthesis will be provided after the revised scope in a research protocol published on the Open Science Framework website (https://osf.io/7awvd/).

Populations

The population of focus for the review is women seeking relief from vasomotor symptoms associated with menopause.

Data permitting, we will evaluate the evidence for subpopulations defined by:

- Sociodemographic factors (e.g., age, race, and ethnicity)
- Weight/BMI
- Women who are not eligible for menopausal hormone therapy due to contraindications (e.g., history of breast cancer, blood clots etc.)
- Women who have experienced surgical menopause

Interventions

The intervention of interest for this review is

- Fezolinetant (Astellas Pharma Inc.)

Comparators

Data permitting, we intend to compare fezolinetant to:

- No medical therapy (as estimated by the placebo arm of clinical trials)
- Menopausal Hormone Therapy
- Estrogen and progestin or progesterone
- Estrogen only
- SSRIs/SNRIs, potentially focusing on the most effective agents if there is evidence of variable effects within the class
- Gabapentin
- Pregabalin

Outcomes

The outcomes of interest are described in the list below.

- Patient-Important Outcomes
    - Frequency and severity of vasomotor symptoms
    - Sleep quality
    - Quality of life
    - Interference of symptoms with daily life
    - Functional impairment (e.g., work productivity)
    - Other menopausal symptoms
        - Vaginal symptoms
        - Urinary tract symptoms
        - Sexual function
    - Other patient-reported outcomes
        - Mood changes
- Adverse events (AEs) including but not limited to
    - Serious AEs
    - Discontinuation due to AEs
    - Other AEs including but not limited to
        - Endometrial hyperplasia or cancer
        - Bone density markers (e.g., fractures, osteoporosis)
        - Breast cancer
        - Coronary heart disease
        - Venous thromboembolism (e.g., pulmonary embolism)
        - Stroke
        - Colorectal cancer
        - Liver toxicity (e.g., AST and ALT levels)
        - All-cause mortality
        - Suicidality

Timing

Evidence on intervention effectiveness and evidence on harms will be derived from studies of any duration.

Settings

Vasomotor symptoms associated with menopause are generally treated in outpatient and/or clinic settings, which will be the focus of our review.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on potential other benefits offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. These general elements (i.e., not specific to a given disease) are listed in the table below.

Table 1.2. Categories of Contextual Considerations and Potential Other Benefits or Disadvantages

Contextual Consideration*
Acuity of need for treatment of individual patients based on short-term risk of death or progression to permanent disability
Magnitude of the lifetime impact on individual patients of the condition being treated
Other (as relevant)

*Contextual considerations refer to social or ethical priorities that shape to some extent how the value of any effective treatments for a particular condition will be judged.

Potential Other Benefit or Disadvantage*
Patients' ability to achieve major life goals related to education, work, or family life
Caregivers' quality of life and/or ability to achieve major life goals related to education, work, or family life
Patients' ability to manage and sustain treatment given the complexity of regimen
Society's goal of reducing health inequities
Other (as relevant)

*Potential other benefits or disadvantages are meant to reflect the broader effects of a specific treatment on patients, caregivers, and society.

ICER encourages stakeholders to provide input on these elements in their public comment submissions.

Scope of Comparative Value Analyses

As a complement to the evidence review, we will develop an economic model to assess the lifetime cost-effectiveness of the treatments of interest relative to no medical therapy (as estimated by the placebo arms of clinical trials) and to relevant comparator treatments. The model structure will be based in part on a literature review of prior published models of menopause. The base-case analysis will take a health care system perspective (i.e., focus on direct medical care costs only). Data permitting, productivity impacts and other indirect costs will be considered in a separate analysis. This modified societal perspective analysis will be considered as a co-base case when the societal costs of care are large relative to direct health care costs, and the impact of treatment on these costs is substantial. This will most often occur in cases where the incremental cost-effectiveness ratio changes by greater than 20%, greater than $200,000 per QALY, and/or when the result crosses the threshold of $100,000 - $150,000 per QALY gained. The target population will consist of women with VMS associated with menopause. The model will consist of health states that define symptom relief and may include a range of longer-term health outcomes given available

evidence. A cohort of patients will transition between states during predetermined cycles of length tied to clinical trial duration over a lifetime time horizon, modeling patients from treatment initiation until death. We will explore treatment durations that are defined by average duration of VMS. In addition, cost-effectiveness will be estimated for shorter time horizons (e.g., five years).

Key model inputs will include clinical probabilities, quality of life values, and health care costs. Probabilities, costs, and other inputs will differ to reflect varying effectiveness between interventions. Treatment effectiveness will be estimated using evidence from fezolinetant trials and relevant comparators.

Health outcomes and costs will be dependent on time spent in each health state, clinical events, adverse events (AEs), and direct medical costs. The health outcome of each intervention will be evaluated in terms of symptom improvements (e.g., using the Menopause-Specific Quality of Life (MENQOL) Questionnaire), life-years gained, quality-adjusted life years (QALYs) gained, and equal value of life years (evLYs) gained. Quality-of-life weights will be applied to each health state, including quality-of-life decrements for reasons such as serious adverse events. The model will include direct medical costs, including but not limited to costs related to drug administration, drug monitoring, condition-related care, and serious adverse events. In addition, productivity changes and other indirect costs will be included in a separate analysis if available data allow. Relevant pairwise comparisons will be made between treatments, and results will be expressed in terms of the incremental cost per QALY gained, cost per evLY gained, cost per life-year gained, and cost per day with symptom improvement.

In separate analyses, we will explore the potential health care system budgetary impact of treatment over a five-year time horizon, utilizing published or otherwise publicly-available information on the potential population eligible for treatment and results from the economic model for treatment costs and cost offsets. This budgetary impact analysis will indicate the relation between treatment prices and level of use for a given potential budget impact and will allow assessment of any need for managing the cost of such interventions. More information on ICER's methods for estimating potential budget impact can be found here.

Identification of Low-Value Services

ICER includes in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see ICER's Value Assessment Framework). These services are ones that would not be directly affected by fezolinetant (e.g., prescription of other medications for VMS), as these services will be captured in the economic model. Rather, we are seeking services used in the current management of vasomotor symptoms beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services

(including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

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