Elagolix for Endometriosis

Public Meeting – Afternoon Session
July 12, 2018

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIFI Network: Student
Password: [Open network]
Welcome and Introduction

Why are we here this afternoon?

[T]here is an important unmet need to treat patients with symptomatic endometriosis. With no cure or innovations for the past two decades, new diagnostic and therapeutic options have the potential to improve a woman’s health status significantly and thus reduce the social and economic burdens associated with this disease, including medical expenses.

- Society for Women’s Health Research

About 1 in 10 women suffer from endometriosis during their reproductive years, so an approval could generate annual sales well into the 9-figures. Elagolix’s total market opportunity could be even bigger than that: AbbVie released positive data for the drug from the first of two uterine fibroid trials on Feb. 21, and on Tuesday, it reported positive data from the second.

- The Motley Fool, March 13 2018
Welcome and Introduction

Why are we here this afternoon?

• Increasing health care costs affecting individuals, state and federal budgets

• New mechanisms of action often raise questions about appropriate use, cost

• Patients can have difficulty accessing drugs
  – Step therapy protocols
  – Requirements to switch drugs with new insurance
  – High out-of-pocket costs

• Need for objective evaluation and public discussion of the evidence on effectiveness and value
Welcome and Introduction

How was the ICER report on elagolix developed?

• Scoping with guidance from patient groups and advocates, clinical experts, manufacturers, and other stakeholders
• Internal ICER staff evidence analysis
• University of Colorado – Denver cost-effectiveness modeling
• Public comment and revision
• Expert report reviewers
  – Dr. John Petrozza, Chief, Division of Reproductive Medicine and IVF; MGH
  – Casey Berna, Endometriosis Advocate
• How is the evidence report structured to support CEPAC voting and policy discussion?
Goal: Sustainable Access to High-Value Care for All Patients

Long-Term Value for Money
- Comparative Clinical Effectiveness
- Incremental cost-effectiveness
- Other Benefits or Disadvantages
- Contextual Considerations

Short-Term Affordability
- Potential Budget Impact
Afternoon Agenda

1:00 pm: Welcome and Opening Remarks
1:10 pm: Presentation of the Evidence and Economic Modeling
  • Steven J. Atlas, MD, MPH, Director, Primary Care Research and Quality Improvement Network, Massachusetts General Hospital
  • R. Brett McQueen, PhD, University of Colorado - Denver

2:10 pm: Public Comments
2:30 pm: NE CEPAC Vote on Clinical Effectiveness and Value

3:15 pm: Policy Roundtable Discussion
4:45 pm: Reflections from Experts and NE CEPAC Panel
5:00 pm: Meeting Adjourned
Evidence Review

Steven J. Atlas, MD, MPH
Director, Primary Care Research and Quality Improvement Network
Massachusetts General Hospital
Key review team members:
Geri Cramer, BSN, MBA
Patricia Synnott, MALD, MS
Leslie Xiong, BS

Disclosures:
We have no conflicts of interest relevant to this report.
Topic in Context

• Endometriosis is a chronic gynecological condition characterized by the attachment and proliferation of endometrial-like tissue outside of the uterus
• Symptoms vary in severity and include painful menstrual periods (dysmenorrhea), nonmenstrual pelvic pain, pain during intercourse (dyspareunia)
• Affects 6-10% of women of reproductive age, with peak prevalence between 25 to 35 years of age
• Estimated population in the United States: 4-10 million women
Therapies for Endometriosis

• Available medical and surgical treatments can decrease symptoms, but none offer long-term relief

• Initial therapy often includes nonsteroidal anti-inflammatory drugs and hormonal contraceptives

• FDA approved gonadotropin-releasing hormone (GnRH) agonists used as a second line treatment
  • Only available by injection or intranasal administration
  • Initially stimulates pituitary gland to release female hormones and can worsen symptoms during first 2 weeks

• Elagolix is a short-acting, oral, nonpeptide, GnRH antagonist under review by FDA
  • Rapidly suppresses the pituitary-ovarian hormones and produces dose-dependent estrogen suppression
Endometriosis from a Patient Perspective

• Symptoms can affect patient’s quality of life by increasing depressive symptoms, reducing sexual satisfaction, and disrupting personal relations

• Misperception that endometriosis is “bad menstrual cramps” leads to under-appreciating its impact, including work and family issues

• Lack of sufficient awareness by clinicians may account for delays in diagnosis as well as not enough research looking for new therapies

• Some patients concerned that elagolix use may end up delaying potentially beneficial surgery
Scope of the Review

• To evaluate the comparative clinical effectiveness of elagolix for symptomatic endometriosis

• Comparators:
  • Placebo (no treatment), GnRH agonists, hormonal contraceptives, aromatase inhibitors

• Key outcomes & harms

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysmenorrhea</td>
<td>Low estrogen side effects</td>
</tr>
<tr>
<td>Nonmenstrual pelvic pain</td>
<td>Bone mineral density changes</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Lipid profile changes</td>
</tr>
<tr>
<td>Use of analgesics</td>
<td>Congenital malformations</td>
</tr>
</tbody>
</table>
Body of Evidence

• Five trials of elagolix
  • 2 Phase III RCTs, 3 Phase II
  • 4/5 studies included a placebo arm
  • 2/5 included active-controls:
    • Depot medroxyprogesterone acetate (DMPA)
    • GnRH agonist: Leuprorelin acetate

• Key differences across studies
  • Dosing of elagolix
  • Populations: Time since diagnosis, BMI
  • Outcomes: choice of endpoints and method of assessment
# Overview of Randomized Trials

<table>
<thead>
<tr>
<th>Key Trials</th>
<th>Treatment Groups</th>
<th>Patient Characteristics</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EM-I</td>
<td>Placebo</td>
<td>N=872</td>
<td>Clinical Response</td>
</tr>
<tr>
<td>Phase III</td>
<td>Elagolix 150 QD</td>
<td>Median age: 31</td>
<td></td>
</tr>
<tr>
<td>Parallel-arm RCT</td>
<td>Elagolix 200 BID</td>
<td>BMI (kg/m²): 28</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM-II</td>
<td>Placebo</td>
<td>N=817</td>
<td>Clinical Response</td>
</tr>
<tr>
<td>Phase III</td>
<td>Elagolix 150 QD</td>
<td>Median age: 33</td>
<td></td>
</tr>
<tr>
<td>Parallel-arm RCT</td>
<td>Elagolix 200 BID</td>
<td>BMI (kg/m²): 27</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tulip PETAL</td>
<td>Placebo</td>
<td>N=174</td>
<td>Multiple pain measures</td>
</tr>
<tr>
<td>Phase II</td>
<td>Elagolix 150 QD</td>
<td>Mean age: 31</td>
<td></td>
</tr>
<tr>
<td>Parallel-arm RCT with crossover</td>
<td>Elagolix 250 QD</td>
<td>BMI (kg/m²): 23</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leuprorelin acetate 3.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PETAL</td>
<td>DMPA-SC</td>
<td>N=252</td>
<td>Change in BMD</td>
</tr>
<tr>
<td>Phase II</td>
<td>Elagolix 150 QD</td>
<td>Mean age: 32</td>
<td></td>
</tr>
<tr>
<td>Parallel-arm RCT</td>
<td>Elagolix 75 BID</td>
<td>BMI (kg/m²): 26</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lilac PETAL</td>
<td>Placebo</td>
<td>N=155</td>
<td>Change in monthly pelvic pain</td>
</tr>
<tr>
<td>Phase II</td>
<td>Elagolix 150 QD</td>
<td>Mean age: 31</td>
<td></td>
</tr>
<tr>
<td>Parallel-arm RCT</td>
<td>Elagolix 250 QD</td>
<td>BMI (kg/m²): 27</td>
<td></td>
</tr>
</tbody>
</table>
Key clinical outcomes

• Primary Outcome:
  • Patient Reported Clinical Response (%)
    • Stable or reduced analgesic use and
    • Clinically meaningful reduction in 1) dysmenorrhea, or 2) nonmenstrual pelvic pain

• Secondary Outcomes:
  • Single item pain questions
    • Numeric rating scale: 11-point response
    • Biberoglu and Behrman (B&B) scale: 4-point response
  • Weighted average combined response for dysmenorrhea and pelvic pain: derived for CEA model
  • Quality of life
    • Endometriosis Health Profile (EHP-30): 30-item with 4-point response covering 5 domains
Results
# Primary Outcome: Response at 6 months

- Clinical Responders

<table>
<thead>
<tr>
<th></th>
<th>Dysmenorrhea (%)</th>
<th>Nonmenstrual Pelvic Pain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EM-I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>23.1</td>
<td>34.9</td>
</tr>
<tr>
<td>Elagolix 150 QD</td>
<td>42.1</td>
<td>45.7</td>
</tr>
<tr>
<td>Elagolix 200 BID</td>
<td>75.3</td>
<td>62.1</td>
</tr>
<tr>
<td><strong>EM-II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>25.4</td>
<td>40.6</td>
</tr>
<tr>
<td>Elagolix 150 QD</td>
<td>46.2</td>
<td>51.6</td>
</tr>
<tr>
<td>Elagolix 200 BID</td>
<td>76.9</td>
<td>62.2</td>
</tr>
</tbody>
</table>
Secondary Outcomes: Pain Measures

- Statistical improvements in dysmenorrhea and nonmenstrual pelvic pain scores with elagolix compared to placebo

- Weighted average combined response for dysmenorrhea and nonmenstrual pelvic pain
  - 65.6% of 200 mg BID elagolix group vs. 35.3% of placebo group

- Differences between elagolix and active comparators in Phase II trials were not significant or not tested
Key Outcomes: Quality of Life

• Significant improvement in all dimensions of EHP-30 at 3 and 6 months with 200 mg BID elagolix vs. placebo
• 3-4 dimensions improved with 150 QD elagolix vs. placebo in Phase III trials
• Statistically significant improvement with leuprolelin acetate vs. elagolix 150 QD
• No difference in quality of life between DMPA and elagolix
## Harms

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Elagolix 150 mg</th>
<th>Elagolix 200 mg</th>
<th>Leuprorelin Acetate</th>
<th>DMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE leading to DC</td>
<td>6</td>
<td>4 – 6</td>
<td>9 - 10</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>3</td>
<td>1 – 5</td>
<td>2 - 3</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>0.3</td>
<td>3 – 5</td>
<td>6 - 9</td>
<td>98</td>
<td>NR</td>
</tr>
<tr>
<td>Headache</td>
<td>10 - 14</td>
<td>15 - 19</td>
<td>17 - 23</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Hot flash</td>
<td>7 - 10</td>
<td>23 - 24</td>
<td>42 - 48</td>
<td>84</td>
<td>76</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 - 3</td>
<td>6</td>
<td>7 - 11</td>
<td>&lt;5%</td>
<td>5</td>
</tr>
<tr>
<td>Mood swings</td>
<td>2 - 3</td>
<td>4 – 6</td>
<td>3 - 4</td>
<td>NR</td>
<td>12</td>
</tr>
<tr>
<td>Nausea</td>
<td>11 - 14</td>
<td>10 - 12</td>
<td>16</td>
<td>13</td>
<td>16</td>
</tr>
</tbody>
</table>
Other Harms

• Dose-dependent reductions in bone mineral density (BMD) at lumbar spine, femoral neck and total hip
  • 12-13% of 200 mg group lost >8% of BMD after 12 months
  • Not fully return to baseline after discontinuation

• Elevations in total cholesterol, LDL cholesterol, and triglycerides

• Safety of elagolix in pregnancy unknown

• FDA concern about liver function tests
Controversies & Uncertainties

• Differences in dosing and duration, primary endpoints, and outcome analysis across Phase II and III studies

• Elagolix vs. active comparator data from 2 Phase II studies are limited by:
  • Small sample sizes, incomplete reporting and imbalances in baseline characteristics, short duration of follow-up, high attrition, limited statistical testing

• Unable to perform quantitative indirect comparisons of elagolix regimens

• Comparative effectiveness and safety beyond 3-6 months of treatment uncertain
  • Potential long-term harms even after stopping treatment (e.g. BMD decreases persist)
## ICER Evidence Ratings

<table>
<thead>
<tr>
<th>Elagolix</th>
<th>ICER Evidence Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>vs. Placebo</td>
<td>Promising but Inconclusive (P/I)</td>
</tr>
<tr>
<td>vs. GnRH agonists, hormonal contraceptives, or aromatase inhibitors</td>
<td>Insufficient (I)</td>
</tr>
</tbody>
</table>
Potential Other Benefits and Contextual Considerations

• Elagolix is first new treatment in over a decade
• Oral formulation (vs. nasal spray or intramuscular injections with GnRH agonists)
• More rapid reversal of side effects and avoids surge in hormones common with agonists
• But still works by decreased hormone level and isn’t a cure for endometriosis
• Even if helpful, it is uncertain if it be used as a chronic therapy
Cost Effectiveness

R. Brett McQueen, PhD
University of Colorado Anschutz Medical Campus

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INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW
Key Team Members

Melanie D. Whittington, PhD, University of Colorado
Jonathan D. Campbell, PhD, University of Colorado
Sam McGuffin, University of Colorado
Varun Kumar, MPH, MSc, Institute for Clinical and Economic Review
Rick Chapman, PhD, Institute for Clinical and Economic Review

Disclosures:
Financial support was provided to the University of Colorado from the Institute for Clinical and Economic Review.

University of Colorado researchers have no conflicts to disclose defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.
Objective

Estimate the cost-effectiveness of elagolix for the treatment of endometriosis-associated pain in adult, pre-menopausal women.
Methods in Brief
## Base-Case Population

<table>
<thead>
<tr>
<th>Cohort Characteristic (Baseline)</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>32 (18-48) years</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28 ± 6.2</td>
</tr>
<tr>
<td>Score for dysmenorrhea [0 (none) – 3 (severe)]</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>Score for nonmenstrual pain [0 (none) – 3 (severe)]</td>
<td>1.6 ± 0.5</td>
</tr>
<tr>
<td>Score on numeric rating scale [0 (none) – 10 (worst)]</td>
<td>5.5 ± 1.7</td>
</tr>
</tbody>
</table>

*Weighted average of EM-I and EM-II clinical trials
Interventions and Comparators

• **Intervention:** Elagolix 200mg Twice Daily
• **Primary comparator:** No active treatment or usual care (placebo with non-specific rescue analgesics)
Methods Overview

• **Model:** Decision tree & Markov model with combined dysmenorrhea and non-menstrual pelvic pain response

• **Setting:** United States

• **Perspective:** Health sector (direct medical care and drug costs)

• **Time horizon:** 18 Years (until average age of menopause)

• **Discount rate:** 3% per year (costs and outcomes)

• **Cycle Length:** 3 months

• **Primary outcome:** Cost per quality-adjusted life year (QALY) gained

• **Secondary outcome:** Surgeries, cardiovascular disease, fractures
Model Schematic

Decision tree: 0-6 months – assessment of response

Elagolix 200mg Twice Daily

- Response → M1
- No response → M2
  - Discontinue (surgery) → M3
  - Discontinue (AE) → M2

Comparator

- Response → M1
- No response → M2
  - Discontinue (surgery) → M3
  - Discontinue (AE) → M2

Abbreviation:
AE = adverse event

Markov Model: 6 months to end of model (i.e., 50 years of age)

M1: Reduced Pain

M2: Moderate to severe pain (rescue pain agents)

From all states

M6: Death

M3: Surgery (conservative and hysterectomy)

M4: Post surgery (reduced pain)

M5: Post surgery (moderate to severe pain)
Key Assumptions

• Short-run clinical trial evidence used to extrapolate to long-run involves assumptions on discontinuation, benefits of pain reduction, and risks from using elagolix

• Patients not responding to treatment after the first six months were not be re-treated with elagolix

• A constant proportion of women on elagolix each cycle are assumed to be off treatment for attempted and successful pregnancies

• Proportion of women in all post-surgery states incurred the cost of GnRH agonist and combined oral contraceptive add-back therapy

• Treatment acquisition price was assumed via Seeking Alpha ($7,000 annually)
# Parameters: Treatment Response Rates

<table>
<thead>
<tr>
<th></th>
<th>Elagolix 200mg Twice Daily</th>
<th>Comparator (usual care)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response at 6 months [dysmenorrhea]</td>
<td>76.1%</td>
<td>24.2%</td>
</tr>
<tr>
<td>Response at 6 months [nonmenstrual pelvic pain]</td>
<td>62.1%</td>
<td>37.7%</td>
</tr>
<tr>
<td>Weighted average combined response (dysmenorrhea response for 5/28 days and nonmenstrual pelvic pain response for 1-5/28 days)</td>
<td>64.6%</td>
<td>35.3%</td>
</tr>
<tr>
<td>Absolute difference in weighted average response vs. placebo</td>
<td>29.3%</td>
<td>Referent</td>
</tr>
</tbody>
</table>
Other Key Parameters

• Pain recurrence (discontinuation due to lack of efficacy) risk ratio for elagolix vs. placebo

• Discontinuation due to adverse events and surgeries during the 6-month response assessment period for elagolix vs. placebo

• Long-run adverse events were modeled to include osteoporotic fractures and cardiovascular disease
Parameters: Health Utilities

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced pain health state</td>
<td>0.92</td>
<td>0.916</td>
<td>0.924</td>
</tr>
<tr>
<td>Moderate-to-severe pain health state</td>
<td>0.73</td>
<td>0.703</td>
<td>0.756</td>
</tr>
<tr>
<td>Surgical disutility (e.g., laparoscopy) for 3 months</td>
<td>-0.06</td>
<td>-0.031</td>
<td>-0.085</td>
</tr>
<tr>
<td>Surgical disutility (hysterectomy) for 3 months</td>
<td>-0.07</td>
<td>-0.038</td>
<td>0.103</td>
</tr>
<tr>
<td>Loss of fertility disutility (all subsequent post-hysterectomy health states)</td>
<td>-0.07</td>
<td>0.039</td>
<td>0.107</td>
</tr>
</tbody>
</table>
Results
## Long-Run Clinical Outcomes
(18 year time horizon)

<table>
<thead>
<tr>
<th>Outcome (per 1,000 women)</th>
<th>Elagolix 200 mg Twice Daily</th>
<th>Comparator (usual care)</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgeries (e.g., laparoscopy)</td>
<td>368</td>
<td>647</td>
<td>-279</td>
</tr>
<tr>
<td>Surgeries (hysterectomy)</td>
<td>94</td>
<td>169</td>
<td>-75</td>
</tr>
<tr>
<td>Cardiovascular disease cases</td>
<td>16.5</td>
<td>15.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Fractures</td>
<td>0.92</td>
<td>0.08</td>
<td>0.84</td>
</tr>
</tbody>
</table>
## Base-Case Discounted Costs and Outcomes from Model

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Intervention Costs*</th>
<th>Non-Intervention Costs§</th>
<th>Total Costs</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-run results (6 months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg twice daily¶</td>
<td>$3,600</td>
<td>$500</td>
<td>$4,100</td>
<td>0.43</td>
</tr>
<tr>
<td>Comparator (usual care)</td>
<td>$100</td>
<td>$600</td>
<td>$700</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Long-run results (18-year time horizon)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg twice daily¶</td>
<td>$61,800</td>
<td>$15,500</td>
<td>$77,200</td>
<td>11.77</td>
</tr>
<tr>
<td>Comparator (usual care)</td>
<td>$6,000</td>
<td>$20,000</td>
<td>$26,000</td>
<td>11.11</td>
</tr>
</tbody>
</table>

*Elagolix 200 mg twice daily (not during pregnancy) over the duration of the model with addition of NSAID and opioid pain management medication vs. NSAID and opioid pain management medication alone in placebo arm

§ Non-intervention costs include surgical costs, outpatient visits, and long-run adverse event management and treatment costs

¶ Short-run costs and QALYs not discounted

Assumed projected price per pill = $9.70

All costs rounded to the nearest $100
## Base-Case Discounted Incremental Results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>Incremental Cost Effectiveness Ratio (vs. comparator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elagolix 200 mg twice daily</td>
<td>$3,400</td>
<td>0.028</td>
<td>$121,000</td>
</tr>
<tr>
<td><strong>short-run</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elagolix 200 mg twice daily</td>
<td>$51,200</td>
<td>0.663</td>
<td>$77,000</td>
</tr>
<tr>
<td><strong>long-run</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All costs rounded to the nearest $100
Incremental Cost effectiveness Ratios rounded to the nearest $1,000
Results using assumed projected price per pill of $9.70
One-Way Sensitivity Analyses (Long-Run Time Horizon)

Pain recurrence risk ratio for elagolix vs. placebo
Endometriosis-related pain EQ-5D score
Proportion of women on treatment (elagolix)
Absolute difference in response to nonmenstrual pelvic pain (elagolix vs. placebo)
Proportion/duration of menstruation within model cycle
Probability of subsequent surgery
Mean EQ-5D for women in the United States without pain
Loss of fertility disutility (all subsequent hysterectomy states)
Absolute difference in response to dysmenorrhea pain (elagolix vs. placebo)
Proportion of women using add-back therapy

Base case incremental cost-effectiveness ratio: $77,000 per QALY gained.
* The cost of the drug was not varied and was assumed at a per pill price of $9.70 with an annual price of $7,000.
## Probabilistic Sensitivity Analysis Results

<table>
<thead>
<tr>
<th>Proportion of Simulations That Were Cost-Effective</th>
<th>Cost-Effective at $50,000 per QALY</th>
<th>Cost-Effective at $100,000 per QALY</th>
<th>Cost-Effective at $150,000 per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elagolix 200 mg twice daily long-run</td>
<td>0.26%</td>
<td>94.64%</td>
<td>99.62%</td>
</tr>
</tbody>
</table>

* The cost of the drug was not varied and was assumed at a per pill price of $9.70 with an annual price of $7,000.
### Response Definition Scenario Analyses

<table>
<thead>
<tr>
<th>Response definition</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>Incremental Cost Effectiveness Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response to dysmenorrhea only (Elagolix 200 mg twice daily vs. placebo)</td>
<td>$57,400</td>
<td>1.04</td>
<td>$55,000</td>
</tr>
<tr>
<td>Response to nonmenstrual pelvic pain only (Elagolix 200 mg twice daily vs. placebo)</td>
<td>$49,800</td>
<td>0.58</td>
<td>$86,000</td>
</tr>
<tr>
<td>Response to both dysmenorrhea and nonmenstrual pelvic pain (Elagolix 200 mg twice daily vs. placebo)</td>
<td>$43,300</td>
<td>0.78</td>
<td>$55,000</td>
</tr>
</tbody>
</table>

All costs rounded to the nearest $100
Incremental Cost effectiveness Ratios rounded to the nearest $1,000
# Incremental Results for Modified Societal Perspective (Long-Run Time Horizon)

<table>
<thead>
<tr>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>Incremental Cost Effectiveness Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elagolix 200 mg twice daily vs. placebo</td>
<td>$29,900</td>
<td>0.663</td>
</tr>
</tbody>
</table>

All costs rounded to the nearest $100
Incremental Cost effectiveness Ratios rounded to the nearest $1,000
# Annual Threshold Price Results

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Annual Price at $50,000 per QALY</th>
<th>Annual Price at $100,000 per QALY</th>
<th>Annual Price at $150,000 per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elagolix 200 mg twice daily short-run*</td>
<td>$2,900</td>
<td>$5,800</td>
<td>$8,400</td>
</tr>
<tr>
<td>Elagolix 200 mg twice daily long-run</td>
<td>$4,700</td>
<td>$8,800</td>
<td>$12,800</td>
</tr>
</tbody>
</table>

*Represent 6 months duration, as seen in the trials
All costs rounded to the nearest $100
Limitations

• Lack of data on active comparator treatments
• Lack of long-run clinical evidence on discontinuation, benefits of pain reduction, and risks from using elagolix
• Available evidence from trials contributed to our need to calculate weighted average of response based on average menstrual cycle duration
Conclusions

• Findings suggest elagolix may provide marginal increases in quality-adjusted survival over no active medical management (placebo with non-specific rescue analgesics)

• With the evidence available at this time and the projected price, the estimated cost-effectiveness of elagolix 200 mg twice daily falls within the range of $50,000 to $150,000 per QALY gained
Public Comments Summary

• Elagolix for dysmenorrhea and nonmenstrual pelvic pain should be modeled together
• Societal perspective underestimates lost productivity
• Receipt of add-on treatment following surgery should be considered
• Maximum duration of elagolix should be considered
Supplemental Slides
Additional Key Assumptions

- Two time-horizons were estimated to reflect short-run (6mo) and long-run (18yr) use of elagolix.
- Women passing through the surgery state incurred a disutility from surgery.
- Women in post-hysterectomy health states incurred a disutility from the loss of fertility.
- Women responding and staying on elagolix were assumed to have a constant increased risk of CVD and FX (ages 40 – 50 only due to lack of evidence) compared to placebo.
- Transition probabilities for discontinuation due to lack of efficacy differ by treatment arm but not over time.
## Parameters: Transition Probabilities

<table>
<thead>
<tr>
<th>Input parameter</th>
<th>Value(^a)</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain recurrence (discontinuation due to lack of efficacy) risk ratio for elagolix vs. placebo</td>
<td>0.30</td>
<td>0.08</td>
<td>1.06</td>
</tr>
<tr>
<td>Proportion of women on elagolix treatment</td>
<td>0.981</td>
<td>0.83</td>
<td>1.0</td>
</tr>
<tr>
<td>Probability of subsequent surgery (conditional on prior surgery)(^b)</td>
<td>0.0260</td>
<td>0.017</td>
<td>0.037</td>
</tr>
<tr>
<td>Probability of hysterectomy (conditional on prior surgery)(^b)</td>
<td>0.0164</td>
<td>0.009</td>
<td>0.026</td>
</tr>
<tr>
<td>Probability of response to subsequent surgery(^b)</td>
<td>0.4377</td>
<td></td>
<td>Not varied</td>
</tr>
<tr>
<td>Probability of response to hysterectomy(^b)</td>
<td>0.4970</td>
<td></td>
<td>Not varied</td>
</tr>
<tr>
<td>Proportion who discontinued for pregnancy</td>
<td>0.0190</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>Probability of death from hysterectomy surgery(^b)</td>
<td>0.0080</td>
<td>0.004</td>
<td>0.012</td>
</tr>
</tbody>
</table>
## Parameters: Long-Run Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Elagolix 200 mg twice daily(^a)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of women with low bone mineral density on treatment (-1.5 z score or less)</td>
<td>0.041</td>
<td>0.002</td>
</tr>
<tr>
<td>Relative risk of fracture with a 1 SD decrease in bone mineral density (i.e., low bone mineral density)</td>
<td>1.5</td>
<td>(1.36, 1.65)</td>
</tr>
<tr>
<td>Osteoporotic fracture risk for normal bone density (women aged 40-49)(^b)</td>
<td>0.00065</td>
<td>(0.00063, 0.00067)</td>
</tr>
<tr>
<td>Probability of cardiovascular disease(^b,c)</td>
<td>0.00016</td>
<td>0.00015</td>
</tr>
</tbody>
</table>
Public Comment and Discussion
Casey Berna, MSW
Endometriosis and Infertility Patient Advocate

Conflicts of interest:
• None declared
Conflicts of interest:
• None declared
Heather Guidone, BCPA
Patient Advocate; Program Director, Center for Endometriosis Care & Executive Board Member, Endometriosis Research Center

Conflicts of interest:
• None declared
Voting Questions

WIFI Network: Student
Password: [Open Network]
0. What is the name of the folkloric sea monster that allegedly lives in Lake Champlain?

A. Champ
B. The Serpent
C. Richard
D. Dragonfish
Patient Population for all questions:
Adult premenopausal women with symptomatic endometriosis and moderate-to-severe symptoms.
1. Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by no treatment?

A. Yes
B. No
2. Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by the GnRH agonist, leuprorelin acetate?

A. Yes
B. No
3. Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by hormonal contraceptive, depot medroxyprogesterone?

A. Yes
B. No
4. When compared to no treatment, does elagolix offer one or more of the following “potential other benefits”? (select all that apply)

A. Reduced complexity
B. Reduce important health disparities
C. Reduce caregiver/family burden
D. Novel mechanism of action or approach
E. Significant impact on improving return to work/overall productivity
F. Other important benefits or disadvantages.
5. Are any of the following contextual consideration important in assessing long-term value for money? (select all that apply)

A. Care for individuals with condition of high severity
B. Care of individuals with condition with high lifetime burden of illness
C. First to offer any improvement
D. Compared to no treatment, there is significant uncertainty about long-term risk of serious side effects
E. Compared to no treatment, there is significant uncertainty about the magnitude or durability of long-term benefits
F. Other important contextual considerations.
6. Given the available evidence on comparative clinical effectiveness and the incremental cost effectiveness, and considering other benefits and contextual considerations, what is the long-term value for money of elagolix compared with no active treatment?

A. Low  
B. Intermediate  
C. High
Policy Roundtable
<table>
<thead>
<tr>
<th><strong>Endometriosis Policy Roundtable</strong></th>
</tr>
</thead>
</table>
| **Casey Berna, MSW**  
Endometriosis and Infertility Patient Advocate |
| **Heather Guidone, BCPA**  
Patient Advocate; Program Director, Center for Endometriosis Care; Executive Board Member Endometriosis Research Center |
| **William Brewster, MD, FACP, CHIE**  
Vice President  
Harvard Pilgrim Health Care, New Hampshire Market |
| **Nancy Hogue, PharmD**  
Director of Pharmacy Services  
Department of Vermont Health Access |
| **Rebecca Flyckt, MD**  
Director, Fertility Preservation Program, Obstetrics, Gynecology and Women’s Health Institute  
Cleveland Clinic |
| **Elizabeth McGee, MD**  
Professor, Director of Reproductive Endocrinology and Fertility Division, Department of Obstetrics, Gynecology and Reproductive Services  
University of Vermont Larner College of Medicine |
Expert and CEPAC Panel Reflections
Next Steps

• Meeting recording posted to ICER website next week

• Final Report published on/about August 2
  • Includes description of CEPAC votes, deliberation; policy roundtable discussion

• Materials available at
  https://icer-review.org/topic/endometriosis/
Adjourn