WHAT IS ENDOMETRIOSIS?

Endometriosis is a chronic gynecological condition with symptoms that include painful menstrual periods, nonmenstrual pelvic pain, and pain during intercourse, as well as infertility. Endometriosis affects between four and ten million women of reproductive age in the US.

Pain associated with the condition can decrease quality of life by increasing depressive symptoms, reducing sexual satisfaction, and disrupting personal relations.

TREATMENT OPTIONS

Though available treatments have been shown to decrease the severity and frequency of patient symptoms, none appear to offer a cure or long-term relief. A range of treatment options are currently used, including:

- Nonsteroidal anti-inflammatory drugs and hormonal contraceptive therapy
- Gonadotropin-releasing hormone (GnRH) agonists (available by injection or intranasally)
- Aromatase inhibitors
- Various surgical procedures

Elagolix (Orilissa™, AbbVie) was approved in July 2018 for patients with endometriosis. It is a short-acting, oral GnRH antagonist. It works similarly to GnRH agonists, but, unlike agonists, does not cause an initial surge in hormones that can temporarily increase symptoms, and it and does not completely suppress estrogen. Both GnRH agonists and antagonists can cause low estrogen symptoms, such as hot flashes, as well as bone mineral density loss. Since endometriosis-related symptoms recur after stopping treatment, it remains to be determined whether elagolix is safe or effective for long-term use.

Summary

KEY FINDINGS

The New England CEPAC voted that evidence was not adequate to determine whether elagolix offers a net health benefit compared to no treatment, or compared to treatment with either a GnRH agonist (leuprorelin acetate) or a hormonal contraceptive (depot medroxyprogesterone), due to limited and mixed evidence on clinical effectiveness and potential risks.

AFFORDABILITY AND ACCESS ALERT

Given that optimal clinical uptake at current estimated discount prices would lead to five-year costs far in excess of the $915 million threshold ICER is issuing an Access and Affordability Alert for elagolix.

KEY POLICY RECOMMENDATIONS

It is reasonable for insurers to develop prior authorization criteria for elagolix to ensure prudent use, based on known short-term side effects, and the lack of long-term data on safety and efficacy compared to other treatments.

Manufacturers should engage with key stakeholders in a transparent process to evaluate fair pricing of new therapeutics based upon the added clinical benefit to patients.

Patient organizations should band together to seek commitments from government research funding agencies and manufacturers to increase research for common conditions affecting women's health such as endometriosis.

Clinical Analyses

ICER EVIDENCE RATINGS

How strong is the evidence that elagolix improves outcomes in patients with endometriosis?

Evidence on elagolix compared to no treatment was promising but inconclusive. While important clinical benefits in pain reduction were observed, potentially serious adverse events, such as increased bone mineral density loss and changes in cholesterol levels have not been fully evaluated. The FDA prescribing information also highlighted warnings about elevated liver function tests, suicidal ideation, and reduced ability to recognize pregnancy; therefore, the possibility of net harm cannot be ruled out.

Evidence on elagolix compared to GnRH agonists, hormonal contraceptives, and aromatase inhibitors was insufficient to judge the net health benefit.

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

Elagolix Compared to Placebo		
Menstrual Pain	**Nonmenstrual Pelvic Pain**	**Quality of Life**
↓	↓	↑

High dose elagolix (200 mg twice daily) provided **greater improvements** in pain, quality of life, and decreased use of rescue opioids than the lower dose of elagolix (150 mg daily).

Elagolix **improved dysmenorrhea** (pain during the menstrual cycle) **to a greater degree than nonmenstrual pelvic pain**–although it provided some benefit for both types of pain.

Compared to other therapies

In two Phase II studies that compared elagolix to other treatments (leuprorelin acetate and depot medroxyprogesterone acetate), outcomes of elagolix at 150 mg daily were similar or inferior to comparator therapies. We found no data on elagolix versus aromatase inhibitors.

Clinical Analyses (continued)

HARMS

The most commonly reported side effects of elagolix are hot flash, headache, and nausea.

Bone mineral density loss is significantly greater than with no treatment, particularly with the 200 mg twice daily dose. Changes in blood lipid profiles (elevated total cholesterol, LDL cholesterol, and triglycerides) may put women at higher risk for cardiovascular events.

The FDA prescribing information includes a warning for elevated liver function tests and specifies that elagolix should not be used by patients with severe liver impairment. It also highlights warning for suicidal ideation and reduced ability to recognize pregnancy.

The safety of elagolix use during pregnancy is uncertain.

SOURCES OF UNCERTAINTY

Trial Designs: Phase II and III studies of elagolix had major differences, including dosing, duration of use, primary endpoints, and outcome analysis. As a result, we were unable to perform indirect comparisons and cost-effectiveness modeling between elagolix and active comparators.

Dosing Effects: The Phase III trials included a 200 mg twice a day dosing regimen that was not evaluated in prior trials. Evidence suggests a dose-response relationship with increased efficacy but also greater side effects.

Duration of Treatment Response: Available evidence has evaluated elagolix versus placebo or active comparators only through three or six months. Given that endometriosis is a chronic condition with no available treatment demonstrating cure or long-term control of symptoms, how elagolix compares to other therapies over time and potentially with long-term use is uncertain.

Outcome Measures: A variety of pain and functional status outcomes were used in the Phase II and III trials of elagolix. The primary patient-reported clinical response outcome of the Phase III trials was not previously used in trials, separate clinical response was reported for dysmenorrhea and nonmenstrual pelvic pain with no overall pain outcome.

Comparator Data: Head-to-head data for elagolix versus comparators are limited to single Phase II studies, which had relatively small sample sizes, incomplete reporting and imbalances in baseline characteristics, short durations of follow-up, high attrition rates, and limited statistical testing.

Long-term Side Effects: There is uncertainty regarding side effects with longer-term use and with respect to potential long-term harms, particularly decreases in bone mineral density that did not return to pre-treatment levels even after stopping treatment.

Economic Analyses

LONG-TERM COST-EFFECTIVENESS

At the assumed net price of $7,400, elagolix falls within commonly accepted thresholds for cost-effectiveness of $50,000-$150,000 when compared to other pain medications.

Elagolix 200 mg twice daily, short-run:

$126,800/QALY*

Elagolix 200 mg twice daily, long run:

$81,000/QALY

**QALY: quality-adjusted life year*

Elagolix's cost-effectiveness was analyzed using a short-term decision tree (6 months) as well as a long-term (18 year) model in keeping with the average age of treatment initiation to menopause. Elagolix was modeled at the 200mg dose to capture the larger clinical benefit demonstrated in the trials; however, this was also associated with higher rates of side effects.

VALUE-BASED PRICE BENCHMARKS

What is a fair price for elagolix based on its value to patients and the health care system?

	ANNUAL WAC	ANNUAL PRICE TO ACHIEVE $100,000 PER QALY THRESHOLD	ANNUAL PRICE TO ACHIEVE $150,000 PER QALY THRESHOLD	DISCOUNT FROM WAC REQUIRED TO REACH THRESHOLD PRICES
Elagolix 200 mg Twice daily *Short-run**	$10,138	$5,800	$8,400	43% to 17%
Elagolix 200 mg Twice daily *Long-run**	$10,138	$8,800	$12,800	14% to +26%

**Economic analysis were conducted using a short-term decision tree (6 months) as well as a long-term (18 year) model in keeping with the average age of treatment initiation to menopause.*

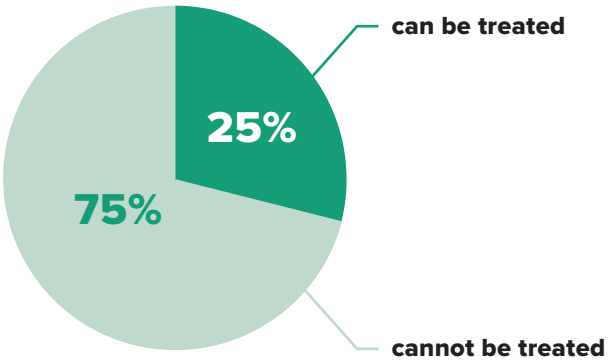
Economic Analyses (continued)

How many patients can be treated with elagolix before crossing ICER's $915 million budget impact threshold?

POTENTIAL SHORT-TERM BUDGET IMPACT

The annual budget impact of treating the entire eligible population at elagolix's assumed net price ($7,400) was estimated at approximately $3.7 billion. The per patient budget impact versus other pain medications was approximately $4,800.

At elagolix's assumed net price, however, only 25% of the eligible population cohort could be treated each year before the budget exceeded the ICER annual budget impact threshold of $915 million.



AFFORDABILITY AND ACCESS ALERT

Given that optimal clinical uptake at current estimated discount prices would lead to five-year costs far in excess of the $915 million threshold ICER is issuing an Access and Affordability Alert for elagolix.

ICER's Access and Affordability Alert is intended to provide a signal to manufacturers, insurers, patient groups, and other stakeholders when the amount of added health care costs associated with these new treatments may be difficult for the health care system to absorb over the short term without displacing other needed services or contributing to rapid growth in health care insurance costs that threaten sustainable access to high-value care for all patients. ICER encourages all stakeholders to consider whether action should be taken to achieve additional price discounts, prioritize treatment access, find ways to reduce waste to provide additional resources, or take other policy steps to manage these budget implications.

Voting Results

The New England CEPAC deliberated on key questions raised by ICER's report at a public meeting on July 14, 2018. More detail on the voting results is provided in the full report.

CLINICAL EFFECTIVENESS

During the meeting, the council voted that evidence was not adequate to determine whether elagolix offers a net health benefit compared to no treatment, or compared to treatment with either a GnRH agonist (leuprorelin acetate) or a hormonal contraceptive (depot medroxyprogesterone), due to limited and mixed evidence on clinical effectiveness and potential risks.

LONG-TERM VALUE FOR MONEY

The council did not vote on value, due to their finding that evidence is inadequate to determine that the clinical benefits of elagolix outweigh its unknown long-term risks.

OTHER POTENTIAL BENEFITS AND CONTEXTUAL CONSIDERATIONS

During the deliberation, panel members discussed the broader considerations around the significant impact endometriosis can have on women's quality of life, elagolix's availability as an oral agent, as well as other unique characteristics of the drug. They also noted the the uncertainty around the therapy's long-term side effects and clinical benefit, as elagolix use was limited to 6-12 months in clinical trials yet therapy intended to treat a chronic and disabling condition.

Policy Roundtable

The Midwest CEPAC participated in a moderated policy discussion that included physicians, patient advocates, manufacturer representatives, and payer representatives. None of the resulting policy statements should be taken as a consensus view held by all participants. For a more detailed discussion, please see the full report.

PAYERS

It is reasonable for insurers to develop prior authorization criteria for elagolix to ensure prudent use, based on elagolix's known short-term side effects, and the lack of long-term data on safety and efficacy compared to other well-established treatments.

Prior authorization criteria should be based on clinical evidence, with input from clinical experts and patient groups. Options for specific elements of coverage criteria within insurance coverage policy include:

- **Potential patient eligibility criteria:** Premenopausal women with symptomatic endometriosis who have had inadequate relief after at least three months of first-line therapy with nonsteroidal anti-inflammatory meds (NSAIDs) and hormonal contraceptives.
- **Potential provider criteria:** Prescription only by a specialist in obstetrics/gynecology or reproductive endocrinology. Insurers should, however, consider the potential impact on access for some patients and consider options such as generalist consultation with specialists through telehealth.
- **Potential limitations on initial length of coverage:** Given the importance of monitoring for side effects, the initial coverage period may be limited to a prespecified period of time, e.g. six months, with requirements for clinical attestation of improvement and documentation of monitoring for lipid levels and bone density.

MANUFACTURERS

Manufacturers should engage with key stakeholders in a transparent process to evaluate fair pricing of new therapeutics based upon the added clinical benefit to patients.

Manufacturer-sponsored research should enroll patients who reflect the population of patients commonly encountered in clinical practice and who are most likely to benefit from treatment.

Manufacturers and researchers in endometriosis owe patients, clinicians, and insurers better information on the long-term comparative clinical effectiveness and value of innovative new therapies. They should take action to ensure that future studies directly compare elagolix with other treatment options using standardized research protocols that focus on outcomes that matter most to patients.

PATIENT ORGANIZATIONS

Patient organizations should band together to seek commitments from government research funding agencies and manufacturers to increase research, both basic and clinical, for common conditions affecting women's health such as endometriosis.

Policy Roundtable (continued)

PROFESSIONAL SOCIETIES

Professional societies should take steps to address and minimize potential conflicts of interest and to collaborate with patients and methodological experts on development of comprehensive, unbiased guidelines and educational outreach for patients with endometriosis.

REGULATORS

Regulators should require post-approval, long-term comparative outcomes studies for treatments, like elagolix, that are initially evaluated and approved in short-term randomized trials but for which long-term therapy would be expected for some patients.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care. For more information about ICER, please visit ICER's website (www.icer-review.org).