Elagolix for Treating Endometriosis

Final Evidence Report

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About ICER

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The New England CEPAC is an independent committee of medical evidence experts from across New England, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Council members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about New England CEPAC is available at http://icer-review.org/programs/new-england-cepac/.

The findings contained within this report are current as of the date of publication. Readers should be aware that new evidence may emerge following the publication of this report that could potentially influence the results. ICER may revisit its analyses in a formal update to this report in the future.

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For a complete list of stakeholders from whom we requested input, please visit:
https://icer-review.org/material/elagolix-stakeholder-list/

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List of Acronyms Used in this Report

ACOG	American College of Obstetricians and Gynecologists
AE	Adverse event
ASRM	American Society for Reproductive Medicine
B&B	Biberoglu and Behrman Scale
BID	Bis in die (twice a day)
BMD	Bone mineral density
BMI	Body mass index
CPSSS	Composite pelvic signs and symptoms score
DMPA-SC	Subcutaneous depot medroxyprogesterone acetate
DYS	Dysmenorrhea
EHP	Endometriosis health profile
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-Releasing Hormone
LA	Leuprorelin acetate
LH	Luteinizing hormone
MCID	Minimal clinically important difference
NICE	National Institute for Health and Care Excellence
NMPP	Nonmenstrual Pelvic Pain
NNT	Number needed to treat
NRS	Numeric Rating Scale
NSAID	Nonsteroidal anti-inflammatory drug
OCP	Oral contraceptive pill
PGIC	Patients' Global Impression of Change
PICOT	Population, Intervention(s), Comparator(s), Outcome(s), Timing
PO	Per os (orally)
QD	Quaque die (once a day)
RCT	Randomized controlled trial
SAE	Serious adverse event
SRDR	Systematic Review Data Repository
VAS	Visual Analogue Scale

Executive Summary

Background

Endometriosis is a chronic gynecological condition characterized by the attachment and proliferation of endometrial-like tissue outside of the uterus.[1] Endometriosis affects 6-10% of women of reproductive age, with peak prevalence between 25 to 35 years of age, and is estimated to affect four to 10 million women in the United States.[2-4] Common symptoms of endometriosis include painful menstrual periods, nonmenstrual pelvic pain, pain during intercourse (dyspareunia) and infertility.[1] Pain associated with endometriosis can decrease a patient's quality of life by increasing depressive symptoms, reducing sexual satisfaction, and disrupting personal relations.[5,6] It results in estimated health care costs of over $10,000 per patient per year in the United States and over $15,000 per patient per year in lost work productivity.[7,8]

Definitive diagnosis requires direct visualization at the time of surgery, and delays in diagnosis are common and may contribute to the burden of pain, infertility and quality of life.[5] Though available medical and surgical treatments have been shown to decrease the severity and frequency of patient symptoms, none appear to offer a cure or long-term relief.[9,10] Initial treatment of endometriosis often includes a trial of nonsteroidal anti-inflammatory drugs and hormonal contraceptive therapy.[11] Gonadotropin-releasing hormone (GnRH) agonists represent a second line hormonal treatment because of potential side effects and increased bone loss.[12] Surgery is another common treatment option for women with symptomatic endometriosis, and may occur at the time of a diagnostic laparoscopy or after an insufficient response to medical therapy.[13,14] Surgical treatment is also considered for infertility associated with endometriosis.[15] Inadequate control of pain due to endometriosis may result in chronic opioid use with its known risks. Given the limitations of currently available treatments, new therapies are needed. A new agent, elagolix (Orilissa™, AbbVie) was approved by the FDA for the management of moderate-to-severe pain associated with endometriosis on July 23, 2018.[16]

Elagolix is a short-acting, oral, nonpeptide, GnRH antagonist that rapidly suppresses the pituitary-ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production that varies from partial to full suppression depending on the frequency and dose given.[17,18] In contrast, GnRH agonists act by initially stimulating the pituitary gland to release female hormones and can worsen symptoms of endometriosis during the first 10 to 14 days of treatment before persistent binding to the GnRH receptor leads to full suppression of ovarian hormones. By not producing the initial surge in LH and FSH associated with GnRH agonists, elagolix does not result in an initial increase in symptoms and the need to treat with hormonal contraceptives. Moreover, GnRH agonists must be administered by injection or intranasally, whereas elagolix is an oral medication. The potential for elagolix to produce partial suppression at lower doses may decrease

endometriosis-related pain while minimizing the hypoestrogenic side effects that limit long-term treatment with agents that fully suppress ovarian hormones. The low estrogen state induced by both GnRH agonists and antagonists leads to the main side effects including hot flashes, vaginal dryness, decreased libido, mood swing and headache, as well as decreasing bone density with prolonged use. Because all hormonal agents are associated with recurrent endometriosis-related symptoms after stopping, whether elagolix may be safer or more effective for long-term use remains to be determined.

Insights Gained from Discussions with Patients and Patient Groups

Discussions with individual patients and patient advocacy groups identified several important insights. Key areas of concern included a seeming lack of sufficient awareness of endometriosis on the part of clinicians that may account for delays in diagnosis as well as the research community and industrial partners in searching for new therapies for endometriosis and better measures to assess outcomes of treatment. We note that these themes may not represent the experiences of all patients with endometriosis, particularly those who are less burdened by the condition.

For many women with pelvic pain symptoms, there is a long delay before a diagnosis is made.

- Though some delay may be related to using initial non-steroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives, the many years on average before a definitive diagnosis is made suggests other factors.
- Better diagnostic tests are needed because at present definitive diagnosis can only be made at the time of laparoscopic surgery.
- Clinicians and patients may be reticent to perform surgery in symptomatic individuals.
- Nevertheless, the six to 10 years between onset of pain and surgical diagnosis[19,20] suggests that clinicians may be slow to consider or are not sufficiently aware of the issues in evaluating and diagnosing endometriosis.

Endometriosis a chronic condition with therapies that do not offer a cure.

- If symptoms are not controlled with NSAIDs and hormonal contraceptives, the range of treatments, both medical and surgical, all have limitations.
- The lack of therapies that provide long-term relief with few side effects is thought to reflect insufficient knowledge of the underlying cause(s) of endometriosis.
- Though medical therapies focus on suppressing the production of ovarian hormones, even complete suppression does not eliminate symptoms and cause bothersome side effects.
- Risks of long-term use of therapies like GnRH agonists and antagonists include osteoporosis and adverse effects on cholesterol levels.
- Moreover, medical therapies have not been shown to improve fertility rates.

Some favor greater use of surgery and more aggressive procedures.

- Though few studies have compared medical and surgical treatments, professional medical organizations are perceived to favor medical therapies because of industry support.
- There is also uncertainty about the optimal surgical procedures, especially how aggressive they should be in removing observed endometrial-like tissue.
- Studies have shown that adding hormonal therapy after surgery results in better pain control than surgery alone, but have included newer, more aggressive approaches.[21]

Elagolix is a novel agent, but enthusiasm is muted because it still works by lowering hormone levels.

- Elagolix is the first new FDA approved drug for endometriosis in over 20 years, but it highlights a lack of research focused on a basic understanding of what causes endometriosis.
- Currently available outcome measures do not adequately capture the impact of endometriosis on the physical and emotional aspects of quality of life.

A perception that endometriosis is a "bad version of menstrual cramps" leads to an under-appreciation of its impact on affected women's lives, including work and family issues.

Potential Cost-Saving Measures in Endometriosis

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 headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with endometriosis that could be reduced, eliminated, or made more efficient.

Patient advocates felt that increased awareness of endometriosis and it symptoms could lead to more rapid diagnosis. It is possible that preventing the years of symptoms before an accurate diagnosis is made could decrease the cost of care. We did not identify any published recommendations from initiatives such as the Choosing Wisely® campaign that are relevant to this clinical area.

Comparative Clinical Effectiveness

A total of five trials of elagolix met our inclusion criteria. Two of the five studies were Phase III randomized controlled trials (RCTs); the three remaining studies were Phase II placebo- or active-controlled trials.[22-25] An additional reference reported on data from two double-blind 6-month extension studies of the Phase III trials.[26]

Four of the five studies were placebo-controlled trials.[22,24,25] One Phase II study (Tulip PETAL) included the GnRH agonist leuprorelin acetate as an active comparator in addition to a placebo arm; a fifth study, the Phase II PETAL trial, evaluated elagolix in comparison to a hormonal therapy, depot medroxyprogesterone acetate (DMPA-SC), without a placebo arm.[22,23] We found no studies of elagolix versus an aromatase inhibitor. The studies are summarized in Table ES1.

Table ES1. Elagolix Trials

Key Trials	Treatment Duration	Treatment Groups	Patient Characteristics	Primary Outcome
EM-I, 2017[24,26] Phase III Parallel-arm RCT	6 months + 6-month extension	Placebo Elagolix 150 QD Elagolix 200 BID	N=872 Median age: 31 Age range: 18-48 Caucasian: 87% BMI (kg/m^2): 28	Clinical Responders (%) defined as clinically meaningful reduction in DYS or NMPP plus stable or reduced analgesic use
EM-II, 2017[24,26] Phase III Parallel-arm RCT	6 months + 6-month extension	Placebo Elagolix 150 QD Elagolix 200 BID	N=817 Median age: 33 Age range: 18-49 Caucasian: 89% BMI (kg/m^2): 27	Clinical Responders (%) defined as clinically meaningful reduction in DYS or NMPP plus stable or reduced analgesic use
Tulip PETAL[22] Phase II Parallel-arm RCT with crossover	3-month treatment period until placebo and leuprorelin crossover; 3 months continued treatment	Placebo Elagolix 150 QD Elagolix 250 QD Leuprorelin acetate 3.75	N=174 Mean age: 31 (SD 1) Caucasian: 100% BMI (kg/m^2): 23	No primary outcomes-multiple pain measures (NRS/B&B)
PETAL[23] Phase II Parallel-arm RCT	6 months	DMPA-SC Elagolix 150 QD Elagolix 75 BID	N=252 Mean age: 32 (SD 0.6) Caucasian: 81% BMI (kg/m^2): 26	Change in Bone Mineral Density; multiple pain measures evaluated as secondary endpoints
Lilac PETAL[25] Phase II Parallel-arm RCT	3-month treatment period until placebo crossover; 3 months continued treatment	Placebo Elagolix 150 QD Elagolix 250 QD	N=155 Mean age: 31 (SE 1) Caucasian: 81% BMI (kg/m^2): 27	Change in monthly mean pelvic pain NRS

QD=daily; BID= twice a day; BMI=body mass index; DYS=dysmenorrhea; NMPP=nonmenstrual pelvic pain; NRS=numeric rating scale (0-10); B&B= Biberoglu and Behrman (0-3); VAS=visual analog scale (1-100); DMPA-SC=subcutaneous depot medroxyprogesterone acetate

Characteristics of the populations who participated in the Phase II and III trials of elagolix were generally similar, although patients in the Tulip PETAL trial had a lower mean BMI than women in other studies. All studies required participants to have symptomatic endometriosis with a laparoscopically-confirmed diagnosis ranging between 60 weeks and 10 years prior to enrollment.

There were several other important differences across the trials of elagolix that prevented us from performing a quantitative synthesis of results. First, dosing of elagolix differed among the Phase II trials and between the Phase II and Phase III trials; only the 150 mg per day dose was constant among all the trials.[22-25] The two Phase III studies added a new formulation, 200 mg twice a day, which had not been evaluated in prior trials.[24] Second, efficacy outcomes differed across trials. Although all studies included a version of the four-point Biberoglu and Behrman (B&B) pain scale to assess dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP), patient response methods, time of measurement and outcome analyses varied.[27]

Clinical Benefits

Phase III trials of elagolix found statistically significant reductions in dysmenorrhea and nonmenstrual pelvic pain compared to placebo. High dose (200 mg twice daily) elagolix provided greater improvements in pain, quality of life, and decreased use of rescue opioids than 150 mg daily of elagolix. Elagolix improved dysmenorrhea to a greater degree than nonmenstrual pelvic pain and dyspareunia. Two Phase II studies compared elagolix to other treatments (i.e., DMPA-SC and leuprorelin acetate). In these trials, outcomes of elagolix at 150 mg daily were similar or inferior to comparator therapies. We found no data on elagolix versus aromatase inhibitors.

Clinical Response

The primary outcome in the Phase III trials (EM-I and EM-II) was the proportion of patients with a clinical response at three months; six-month data was also reported. Clinical response was defined as a clinically meaningful change in pain score as well as stable or reduced use of analgesics. This outcome was measured separately for dysmenorrhea and nonmenstrual pelvic pain, and minimal clinically important differences were derived quantitatively in each study. The criteria used to define a clinically meaningful reduction in symptoms had not been previously used or validated. Table ES2 reports the proportion of women with a clinical response in both trials at six months (three-month data can be found in the full report).

Table ES2. Proportion of Women with a Clinical Response in EM-I and EM-II

		Dysmenorrhea (%)*	Nonmenstrual Pelvic Pain (%)*
		6 Months	6 Months
EM-I[24]	Placebo	23.1	34.9
	Elagolix 150 QD	42.1	45.7
	Elagolix 200 BID	75.3	62.1
EM-II[24]	Placebo	25.4	40.6
	Elagolix 150 QD	46.2	51.6
	Elagolix 200 BID	76.9	62.2

*Elagolix 150 mg QD and 200 mg BID were statistically better ($p<0.05$) than placebo at 3 and 6 months; QD=once daily; BID=twice daily

Approximately three quarters of women taking the high dose of elagolix (200 mg twice daily) reported a clinical response for dysmenorrhea at six months. This represented an absolute difference from placebo of 52% (97.5% CI, 44 to 60).[24] Higher response rates were also seen for the 150 mg daily dose treatment arm, but the magnitude of the difference was lower (19-21%). The response to nonmenstrual pelvic pain was lower for the high dose of elagolix, but similar or higher for placebo or the lower dose of elagolix.[24] As a result, the absolute difference from placebo was 22-27% for high dose and 11% for lower dose elagolix.

In a post hoc analysis of combined data from EM-I and EM-II, 56.4% of patients treated with the 200 mg twice daily dose of elagolix achieved a simultaneous response to dysmenorrhea and nonmenstrual pelvic pain at month 6 versus 17.2% of patients treated with placebo; results for the 150 mg daily dose have not been reported.[28]

Other Pain Outcomes

A number of secondary pain outcomes were reported including the numeric rating scale (NRS) for overall endometriosis-associated pain and the B&B scale for dysmenorrhea, nonmenstrual pelvic pain and dyspareunia. Dysmenorrhea and nonmenstrual pelvic pain scores are reported in Table ES3 below. Pain improvements were generally statistically significant with elagolix but not with placebo. However, there is no validated minimal clinically important difference (MCID) for dysmenorrhea and nonmenstrual pelvic pain using this scale.[29,30] Differences between elagolix and its active comparators in Phase II trials were not significant or not tested. Data on NRS and dyspareunia can be found in the full report.

Table ES3. Mean Pain Scores in Randomized Controlled Trials of Elagolix

		Dysmenorrhea			Nonmenstrual Pelvic Pain		
		Baseline	Week 12	Score Change	Baseline	Week 12	Score Change
EM-I[24]	Placebo	2.2	1.9	-0.3	1.6	1.3	-0.3
	Elagolix 150 QD	2.2	1.2	-1.0*	1.6	1.2	-0.4*
	Elagolix 200 BID	2.2	0.4	-1.8*	1.6	0.9	-0.7*
EM-II[24]	Placebo	2.2	1.8	-0.4	1.6	1.2	-0.4
	Elagolix 150 QD	2.2	1.2	-1.0*	1.7	1.1	-0.6*
	Elagolix 200 BID	2.1	0.4	-1.7*	1.6	0.9	-0.7*
Tulip PETAL[22]	Placebo	1.4	0.9	-0.5±	1.0	0.7	-0.3±
	Elagolix 150 QD	1.3	0.5	-0.8±	1.1	0.7	-0.4±
	Leuprorelin acetate	1.3	0.13	-1.2±	0.9	0.4	-0.5±
Lilac PETAL[25]	Placebo	1.2	1.0	-0.2	1.0	0.6	-0.4
	Elagolix 150 QD	1.4	0.6	-0.8*	0.9	0.6	-0.3
PETAL[23]	Elagolix 150 QD	NR	NR	-1.4±	NR	NR	-1.0±
	DMPA-SC	NR	NR	-1.5±	NR	NR	-0.9±

Data were digitized from published charts and should be interpreted with caution; *p<0.05 for LS mean change versus placebo, ±within-arm statistical testing not performed; QD=daily; BID=twice daily; DMPA-SC=subcutaneous depot medroxyprogesterone; NR=not reported

Health Related Quality of Life

In the Phase III trials (EM-I and EM-II), the 200 mg twice daily dose of elagolix provided a statistically significant improvement in all six dimensions of the Endometriosis Health Profile questionnaire (EHP-30) at three and six months compared to placebo.[24] The 150 mg daily dose of elagolix provided quality of life improvement versus placebo at both timepoints on three of six dimensions in EM-I (pain, control and powerlessness, and social support) and four of six dimensions in EM-II (pain, control and powerlessness, emotional well-being and social support).[24] After six additional months of treatment with elagolix in the extension studies (12 months total), improvements were observed across all domains of the EHP-30 in both dose groups, although statistical comparisons between treatment groups were not performed.[26]

In contrast, patients who were treated with leuprorelin acetate reported greater improvements than those treated with 150 mg of elagolix on the EHP-5 quality of life measure.[22] There was no difference in quality of life between elagolix and DMPA-SC.[23]

Analgesic Use

Change from baseline in mean monthly pill counts of NSAIDs and opioids were reported to reflect use of rescue pain analgesics in the Phase III trials. All arms, including placebo, reported reduced analgesic use.[24] At three months, women taking the 200 mg twice daily dose of elagolix reported significantly less opioid use compared to placebo (-0.08 to -0.12, SE 0.03; p<0.01) whereas the 150 mg daily dose did not.[24] In the extension studies, the least squares mean change in opioid pill count from baseline to 12 months was -0.13 to -0.20 in the 150 daily dose group and -0.25 to -0.27 in the 200 twice daily dose group.[26] Statistical comparisons between treatment groups were not performed in the extension studies. Phase II studies showed that there was no difference in rescue analgesic use between the 150 mg daily dose of elagolix and placebo.[22,23,25]

In the Tulip PETAL study of elagolix versus leuprorelin acetate, a greater proportion of women taking leuprorelin acetate reduced their analgesic use as compared to women taking elagolix 150 mg (10.5% vs. 4.4%, respectfully). Statistical significance between these treatment arms was not reported; however, neither treatment was significantly different from placebo (6.2%).[22] The only head-to-head study of elagolix and DMPA-SC showed increased analgesic (opioid) use in all treatment arms.[23]

Harms

The most commonly reported side effects of elagolix are hot flash, headache, and nausea. Bone mineral density (BMD) loss is significantly greater than placebo at the 150 mg daily and especially the 200 mg twice daily dose. After 12 months of continuous treatment without add-back hormonal therapy, 2-8% of women taking the 150 mg once daily dose and 21% taking the 200 mg twice daily dose of elagolix had lost more than 8% of their BMD.[16] Studies did not report how BMD loss translates into future risk of osteoporosis or fracture. 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 also highlighted warnings about elevated liver function tests, suicidal ideation, and reduced ability to recognize pregnancy.

Specific adverse event (AE) frequencies are reported in Table ES4. The most frequently reported AEs in the Phase III trials included hot flash, headache, and nausea.[24] Patients treated with the 200 mg dose of elagolix reported higher rates of hot flash than patients in the 150 mg and placebo groups. Limited data comparing adverse events for patients treated with elagolix and leuprorelin acetate showed similar rates of adverse events over three months.[22] Of note, data for leuprorelin acetate in FDA publications report higher rates of amenorrhea, depression, headache, and hot flash than noted in the elagolix trial.[31]

Table ES4. Adverse Events Occurring During Six Months of Treatment (%)[Δ]

	Placebo[24]	Elagolix 150 mg[24]	Elagolix 200 mg[24]	Leuprorelin Acetate[31,32]*	DMPA-SC[23]
Any AE leading to DC	6	4 – 6	9 - 10	4[α]	17
Any serious AE	3	1 – 5	2 - 3	NR	4
Amenorrhea	0.3	3 – 5	6 - 9	98	NR
Headache	10 - 14	15 - 19	17 - 23	32	18
Hot flash	7 - 10	23 - 24	42 - 48	84	76§
Insomnia	2 - 3	6	7 - 11	<5%	5
Mood swings	2 - 3	4 – 6	3 - 4	NR	12
Nausea	11 - 14	10 - 12	16	13[β]	16

AE=adverse event, DC=discontinuation, NR=not reported Δ Ranges indicate differences between EM-I and EM-II; * AEs of leuprorelin acetate were collected from the FDA Prescribing Information except where otherwise indicated; α Dlugi et al. (1990); β Reported as nausea/vomiting; DMPA-SC=Subcutaneous depot medroxyprogesterone; §All arms of PETAL reported a high proportion of women reporting hot flash.

Women who received placebo and elagolix 150 mg daily in the Phase III trials reported similar rates of discontinuation due to AEs (4.4-6.4%).[24] Approximately 9-10% of women in the 200 mg twice daily arm discontinued study treatment due to adverse effects. Trials of leuprorelin acetate have reported low rates of discontinuation due to AEs (0-2%).[22,33] In the PETAL trial of elagolix versus DMPA-SC, more patients in the DMPA-SC group discontinued therapy due to an adverse event (17% vs. 5% and 8% in the elagolix 150 mg and 75 mg groups, respectively).[23]

Serious AEs were uncommon in the elagolix trials across all intervention arms, although two deaths, not thought related to the drug, were reported in patients treated with elagolix. Changes in bone mineral density and lipid profiles from treatment remain important safety considerations, though it is unknown if these changes will lead to future fractures or cardiac events. Both doses of elagolix significantly reduced bone mineral density at the lumbar spine, femoral neck and total hip compared to placebo in the Phase III trials, with the magnitude being dose dependent.[24] The FDA prescribing information for elagolix includes a warning about dose- and duration-dependent decreases in bone mineral density that may not be reversible.[16]

Data from the FDA prescribing information also included dose-dependent asymptomatic elevations of liver function tests (ALT) that were more common. As a result, elagolix was recommended for 6 months at 150 mg daily in women with moderate hepatic impairment, and contraindicated in women with severe hepatic impairment. In addition, suicidal ideation (including one completed suicide) was seen rarely in patients treated with elagolix but not placebo. To the best of our knowledge, information on these safety concerns have not been published elsewhere.

The safety of elagolix use in pregnant women is unknown and as a result, women were required to use two forms of birth control while participating in clinical trials of elagolix. However, several pregnancies were reported. Among patients treated with elagolix, pregnancy outcomes have

included one spontaneous abortion, one cleft palate, one tracheal fistula, and at least three healthy births. While adverse pregnancy outcomes have not been deemed attributable to elagolix, the company acknowledges that the effect of elagolix on pregnancy is still uncertain.[24,34] Since women using elagolix may become pregnant, the FDA prescribing information warns of reduced ability to recognize pregnancy due to altered menstrual bleeding. Discontinuation of elagolix is recommended if pregnancy is confirmed.[16]

Controversies and Uncertainties

A number of key controversies and areas of uncertainty were identified based upon our clinical evidence review and in developing our cost-effectiveness model with important input from relevant stakeholders. There were major differences between the Phase II and III studies of elagolix including elagolix dosing (total and frequency), duration of use, primary endpoints and outcome analysis and presentation. As a result, we were unable to perform quantitative indirect comparisons and cost-effectiveness modeling for different elagolix regimens or between elagolix and active comparators.

The Phase III trials included a new dosing regimen, 200 mg twice a day, which was not evaluated in prior trials.[22-25] This is the highest daily dose that has been tested, and Phase III trial evidence suggests a dose-response relationship with increased efficacy but also greater side effects. It is also possible that the twice daily dosing regimen may be important. A Phase II trial included a comparison of the same total daily dose given either 150 mg once daily versus 75 mg twice daily. Greater bone density loss with twice daily dosing suggests that frequency of dosing as well as the total dose may be important in assessing drug safety.

Other trial differences in addition to dosing and duration of therapy included outcome measures and how they were analyzed and reported. A variety of pain and functional status outcomes were used in the Phase II and III trials of elagolix. The primary clinical response outcome of the Phase III trials was not previously used in the Phase II trials or any other trial that we identified. Separate clinical response was reported for dysmenorrhea and nonmenstrual pelvic pain, and no attempt was made to report an overall pain outcome reflecting a weighted contribution for each. The co-primary outcomes were based on a composite of a clinically meaningful reduction in pain along with stable or reduced use of analgesics.[24] The calculation of the minimal clinically important difference (MCID) was complex and has not been previously validated. There were other differences in outcome measures between the Phase II and III studies due to changes in the wording and timing of scales in response to changing patient assessment from monthly recall to daily dairy entries.[34] Finally, the presentation of data among the elagolix studies varied in terms of consistency and completeness of baseline variables and follow-up data. This necessitated estimating values by digitizing figures, and needlessly complicated the reporting of trial data.

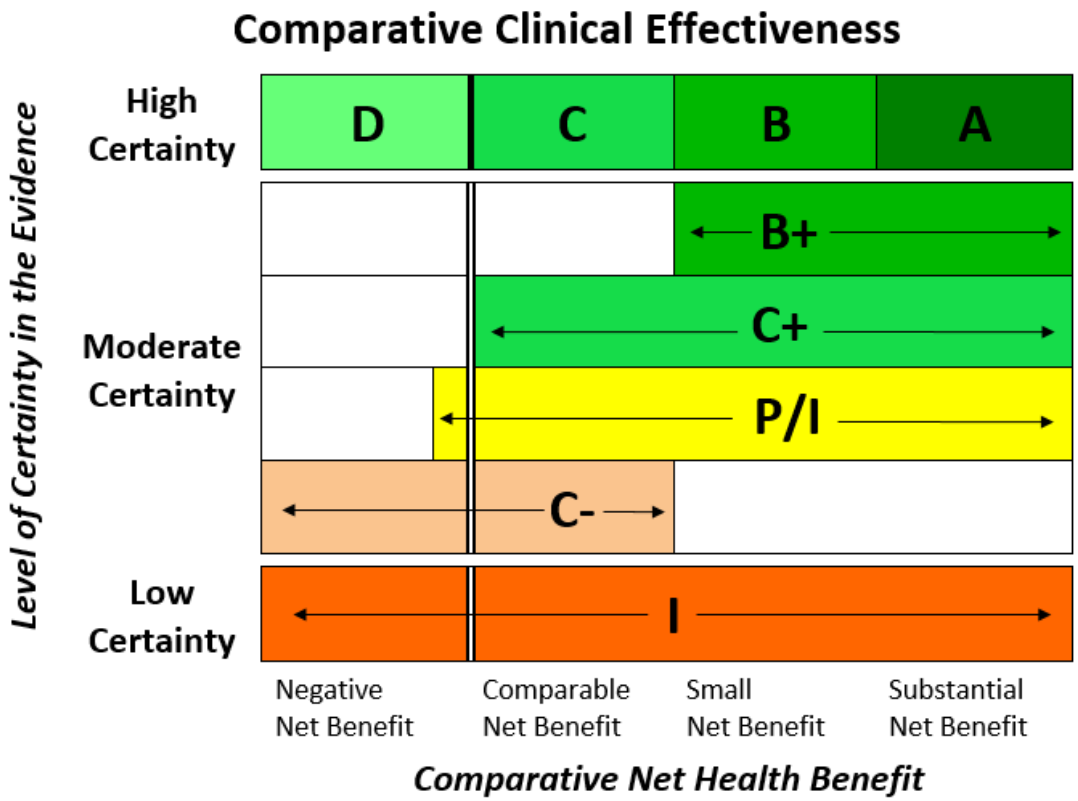
Head-to-head data for elagolix versus the GnRH agonist, leuprorelin acetate, and the progestin, depot medroxyprogesterone acetate was limited to single Phase II studies for each. Limitations of these studies included relatively small sample sizes, incomplete reporting and imbalances in baseline characteristics, short durations of follow-up, high attrition rates and limited statistical testing.[22,23]

The Phase II and III trials of elagolix reported side effects associated with female hormone suppression that were dose-related, but rates of discontinuation were generally low. However, there is uncertainty regarding side effects with longer-term use and with respect to potential long-term harms even after stopping treatment, particularly decreases in bone mineral density (BMD). The dose-dependent suppression of ovarian hormones may permit dosing that improves symptoms while minimizing changes in BMD, but this potential benefit remains uncertain.[35] Studies to date suggest a dose dependent decrease in BMD with elagolix, but the extent to which bone loss is reversible after discontinuation is unknown. While BMD loss is a well-recognized side effect of elagolix, the FDA unexpectedly added three months to its elagolix review timeline due to questions related to liver function tests.[36] Liver toxicity was not reported in the Phase II and III trials of elagolix, but elevated liver function tests data are included in the FDA prescribing information. In addition, the prescribing information mentioned one death due to suicide in a patient treated with elagolix as well as four reports of suicidal ideation among the 2,090 women who were exposed to elagolix during Phase II and III studies. While the death was reported in the publication of the Phase III trials, information related to suicidal ideation was not available in any publication or presentation that we could identify.[16]

Summary and Comment

Using the ICER Evidence Matrix (Figure ES1), we assigned evidence ratings for elagolix relative to alternative therapies for endometriosis-associated pain (Table ES5).

Figure ES1. ICER Evidence Rating Matrix



A* = *"Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B* = *"Incremental" *- High certainty of a small net health benefit*
C* = *"Comparable" *- High certainty of a comparable net health benefit*
D* = *"Negative" *- High certainty of an inferior net health benefit*
B+* = *"Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+* = *"Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I* = *"Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C-* = *"Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I* = *"Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table ES5. ICER Rating on the Comparative Net Health Benefit of Elagolix*

Intervention	Comparator	ICER Evidence Rating
Elagolix	Placebo	P/I
	GnRH agonists	I
	Hormonal Treatments	I
	Aromatase Inhibitors	I

* These ratings were made prior to FDA approval of elagolix.

Elagolix versus Placebo

Compared to placebo, Phase III trials of elagolix (EM-I and EM-II) demonstrated a dose-response effect for dysmenorrhea and nonmenstrual pelvic pain at the two doses of elagolix with statistically significant improvements at three and six months for both doses. In Phase II trials, three months of treatment with elagolix versus placebo led to statistically significant decreases in dysmenorrhea but not nonmenstrual pelvic pain. Secondary pain and quality of life outcomes also demonstrated greater improvement for elagolix compared to placebo. Though use of rescue analgesics decreased more for elagolix compared to placebo, change in opioid use was similar, except at the highest dose of elagolix studied.

Limitations pertaining to outcomes reported in these trials include using a four-point scale to assess pain symptoms (B&B) that is not a true pain scale, was modified for use as a daily measure between the Phase II and III trials, and has no validated clinically meaningful difference. Moreover, the Phase III trials used novel primary outcomes, which consisted of composite measures of a clinical response for either dysmenorrhea or nonmenstrual pelvic pain using the B&B and stable or reduced analgesic use. Clinical response thresholds were defined for each Phase III trial for dysmenorrhea and NMPP. These primary composite outcomes had never been used previously and the individual components were not reported separately, limiting our ability to compare the Phase III results for elagolix to other trials or therapies.

Adverse effects of elagolix were consistent with a dose-dependent hypoestrogenic effect. Though adverse effects were more common with high-dose elagolix (200 mg BID) compared to placebo, few patients discontinued therapy due to adverse side effects in the trials. Nevertheless, potential serious adverse effects such as increased bone loss and changes in cholesterol levels were noted with elagolix compared to placebo. The long-term comparative safety of elagolix is uncertain, and reversal of bone loss and dyslipidemia following discontinuation of elagolix have not been fully evaluated to date. Furthermore, FDA prescribing information includes new information about abnormally elevated markers of liver function and suicidal ideation in patients treated with elagolix.[16,36]

Consequently, despite evidence for improved pain symptoms with elagolix, the possibility of net harm cannot be ruled out at this time. We therefore judge the evidence to be "promising but inconclusive" for the comparison of elagolix to placebo ("P/I").

Elagolix versus GnRH Agonists, Hormonal Contraceptives, and Aromatase Inhibitors

For the comparisons of elagolix versus GnRH agonists, hormonal contraceptives, or aromatase inhibitors, we identified insufficient evidence with which to rate the net health benefit of elagolix. Only single head-to-head trials of elagolix versus leuprorelin acetate and elagolix versus depot medroxyprogesterone were identified, and several aspects of the design of these studies limit our ability to judge their comparative effectiveness. For the comparison of elagolix versus aromatase inhibitors, we did not identify any head-to-head trials or comparative evidence. Thus, we deem there to be insufficient ("I") evidence with which to judge the net health benefit of elagolix versus GnRH agonists, hormonal contraceptives, and aromatase inhibitors.

Long-Term Cost Effectiveness

The primary aim of this analysis was to estimate the cost-effectiveness of elagolix, an oral gonadotropin-releasing hormone (GnRH) antagonist, for the treatment of endometriosis-associated moderate-to-severe pain in adult, pre-menopausal women. The model was structured into two parts: a short-term decision tree and a long-term Markov model. Consistent with the duration of elagolix's pivotal Phase III clinical trials, EM-I and EM-II, the decision tree calculated the costs and consequences of six months treatment of elagolix, including pathways relevant to short-term outcomes, such as response to treatment (i.e. pain reduction).[24] Long-term clinical outcomes, such as pain recurrence, surgeries (laparoscopy and hysterectomy), cardiovascular disease, and fractures were assessed via a Markov model. Quality-adjusted survival and health care costs were estimated for elagolix and comparator treatment using a health sector perspective with the target population age ranging between 32 and 50 years, starting from the average age of treatment initiation[24] and concluding at the average age of menopause.[37] Costs and outcomes were discounted at 3% per year. Incremental costs and outcomes were calculated comparing the intervention to its comparator. While the base case analysis took a health sector perspective, productivity losses at the patient-level were considered in a scenario analysis.

The decision analytic model structure was informed by the primary aim, previous modeling evidence, Phase III clinical trials for elagolix, and stakeholder input. However, relevant comparator information with corresponding and consistent measures to that of Phase III trials was not identified. Our model comparator hence included placebo with non-specific rescue analgesics, henceforth referred to as 'no active treatment'. We found no published economic evaluations of elagolix in treating women with moderate-to-severe endometriosis-related pain. Additionally, high quality evidence concerning long-run clinical evidence on response and discontinuation was sparse. Key model inputs included response to treatment, endometriosis-related pain EQ-5D score,

probability of pain recurrence (discontinuation due to lack of efficacy) for elagolix versus no active treatment, and proportion of women on treatment. Specific to response to treatment, we calculated a weighted average of response based on an average menstrual cycle duration, which weights response by time spent in menstruation (i.e., 5/28 days on average, with variability in sensitivity analyses) within each model cycle length to account for response to pain with and without menstruation. Weighted average response for elagolix was 65.6% versus 35.3% for the comparator. Further detail on model inputs can be found in Section 4 of the full report.

Key model choices and assumptions are detailed below. Please see section 4 of the report for a comprehensive list of model choices and assumptions, and their associated rationale.

Table ES6. Key Model Choices and Assumptions

Assumption	Rationale
Patients not responding to treatment with elagolix after the first six months in the decision tree were not re-treated with elagolix and moved directly to treatment with pain agents and/or surgical procedures.	Re-treatment with elagolix was not attempted for women who did not respond in clinical trials. The re-treatment efficacy of elagolix is unknown.
The proportion of patients responding to treatment in the decision tree model continued on treatment until discontinuation due to lack of efficacy with recurrence to moderate-to-severe pain immediately following discontinuation in the Markov model	Women responding to treatment stayed on treatment to avoid pain recurrence.
Transition probabilities for discontinuation due to lack of efficacy differed by treatment arm (i.e., elagolix and comparator) but did not vary over time.	There was no available evidence on time-varying discontinuation rates for elagolix.
A constant proportion of women on elagolix each cycle was assumed to be off treatment for attempted and successful pregnancies.	Trial evidence showed women discontinued to attempt pregnancy, but there was no evidence suggesting they would permanently discontinue treatment post-delivery.
Women responding and staying on elagolix were assumed to have a constant increased risk for cardiovascular disease and fracture risk as compared to those on no active treatment.	Trial evidence suggested changes in lipid panels and bone mineral density might increase the risk of cardiovascular disease and fractures as compared to age-matched peers not on elagolix.
All states included the cost for treating a proportion of women on NSAID and opioid therapy for pain management. The cost incurred in the pain reduced states is assumed half of the cost of NSAID and opioid therapy use in moderate-to-severe pain health states.	This assumption supports the clinical trial evidence that pain management utilization is likely higher and perhaps twice as high in the moderate-to-severe pain state as compared to the reduced pain state with or without elagolix add-on treatment.
A discount of 27% off the wholesale acquisition cost (WAC) of elagolix was assumed.	A discount off of the WAC of elagolix is expected; however, due to the recent approval of elagolix, an average discount was not able to be estimated using the SSR Health database. Therefore, we assumed a discount of 27% because that is the average discount across all branded pharmaceuticals.
Weighted average combined response to elagolix and no active treatment was assumed for the base case analysis. Specifically, response to dysmenorrhea trial evidence was applied to an average proportion of time of menstruation within each model cycle equal to 5/28. Response to nonmenstrual pelvic pain was applied to the remaining proportion of time (1- 5/28) within each model cycle. Menstruation duration was assumed the same between elagolix and no active treatment.	Trial evidence did not report a combined response metric for dysmenorrhea and nonmenstrual pelvic pain. The combined response assumption weights response by time spent in menstruation within each model cycle length to account for response to pain with and without menstruation. This measure is reflective of not requiring all days to achieve response, but on any selected day. Given that most of the patient's time is spent in a nonmenstrual state, this weighted average is closer to the nonmenstrual pelvic pain treatment response rates.

We used Redbook[38] to identify WACs for pain rescue agents. A discount of 27%, the average discount across all branded pharmaceuticals, from the WAC was assumed for elagolix.[39] The annual WAC and assumed net price for elagolix were $10,138 and $7,400, respectively. Discounts and rebates were not assumed for generic drugs. Cost inputs for other health care services used were obtained from public data sources, as described in section 4 of the report.

Base Case Results

Quality adjusted life years (QALYs) as well as the total discounted costs within six months and an 18-year time horizon are detailed in Table ES7.

Elagolix 200 mg twice daily had a total undiscounted cost of approximately $4,300 with 0.43 QALYs at six months and a total discounted cost of approximately $79,800 and 11.77 QALYs at 18 years. This contrasted with the comparator population (no active treatment), which had a total undiscounted cost of $700 with 0.40 QALYs and a total discounted cost of $26,000 with 11.11 QALYs at six months and 18 years, respectively.

Table ES7. Results for the Base Case Discounted Costs and Outcomes from the Model

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	QALYs
Short-run results (6 months)‡				
Elagolix 200 mg twice daily¶	$3,800	$500	$4,300	0.43
No Active Treatment	$100	$600	$700	0.40
Long-run results (18-year time horizon)				
Elagolix 200 mg twice daily¶	$64,300	$15,400	$79,800	11.77
No Active Treatment	$6,000	$20,000	$26,000	11.11

*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 no active treatment 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

Table ES8 presents the incremental results from the base case analysis, specifically cost per QALY gained versus no active treatment measured in the short-run and in the long-run variation.

Cost per QALY gained for elagolix versus no active treatment was approximately $126,800 and $81,000 for short-run and the long-run time-horizons, respectively.

Table ES8. Base Case Discounted Incremental Results

Intervention	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio (vs. No Active Treatment)
Elagolix 200 mg twice daily *short-run*	$3,600	0.028	$126,800
Elagolix 200 mg twice daily *long-run*	$53,700	0.663	$81,000

Sensitivity Analyses

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for results. Inputs that had the biggest impact on cost-effectiveness ratios include the endometriosis-related pain EQ-5D score, probability of pain recurrence (discontinuation due to lack of efficacy) for elagolix versus no active treatment, and proportion of women on treatment. The probabilistic analysis results indicate a relatively high likelihood of achieving thresholds.

Table ES9. Probabilistic Sensitivity Analysis Results: Elagolix versus No Active Treatment

Proportion of Simulations That Were Cost-Effective			
	Cost-Effective at $50,000 per QALY	**Cost-Effective at $100,000 per QALY**	**Cost-Effective at $150,000 per QALY**
Elagolix 200 mg twice daily *long-run*	0.10%	94.74%	99.68%

Scenario Analyses

The base case health sector perspective was expanded to a modified restricted societal perspective to account for patient-level lost productivity costs over the time horizon. Cost-effectiveness ratios were slightly reduced to $48,900 from including lost productivity estimates as compared to base case ICERs (Please see section 4 for full details on modified societal perspective).

To account for different definitions of response to treatment, we performed three additional scenario analyses specific to response to elagolix and the comparator. Table ES10 presents the incremental costs, incremental QALYs, and incremental cost-effectiveness ratios using response to dysmenorrhea pain only (76.1% elagolix vs. 24.2% no active treatment), response to nonmenstrual pelvic pain only (62.1% elagolix vs. 37.7% no active treatment), and combined response for women who responded to both dysmenorrhea and nonmenstrual pelvic pain (56.41% elagolix vs. 17.19% no active treatment)[28] over the long run horizon. The response definition scenario analyses demonstrated that as incremental response to different or multiple pain symptoms increased from

the use of elagolix relative to no active treatment, the cost-effectiveness ratios were reduced as compared to base case; conversely as incremental response to pain decreases, the cost-effectiveness ratios increased in relation to the base case.

Table ES10. Response Definition Scenario Analyses

Response definition	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio
Response to dysmenorrhea only (Elagolix 200 mg twice daily vs. No Active Treatment)	$60,400	1.04	$58,000
Response to nonmenstrual pelvic pain only (Elagolix 200 mg twice daily vs. No Active Treatment)	$52,300	0.58	$90,000
Response to both dysmenorrhea and nonmenstrual pelvic pain (Elagolix 200 mg twice daily vs. No Active Treatment)	$45,600	0.78	$58,000

QALY: Quality-Adjusted Life Year
All costs rounded to the nearest $100
Incremental Cost effectiveness Ratios rounded to the nearest $1,000

A threshold analysis was also conducted to determine the treatment acquisition cost needed to achieve thresholds of $50,000, $100,000, and $150,000 per QALY gained. Table ES11 presents the threshold annual price results at $50,000, $100,000, and $150,000 per QALY for within-trial and long-run variations, as compared to no active treatment. The threshold analyses suggest what the price would need to be to reach the specific thresholds. Importantly, we note that the short-run timeline is now consistent with the FDA-approved duration of treatment with the 200 mg twice-daily dose of elagolix (six months); it is currently uncertain whether longer-term treatment (possibly with add-back therapy) will occur.

Table ES11. Annual Threshold Price Results

Intervention	Annual Price at $50,000 per QALY	Annual Price at $100,000 per QALY	Annual Price at $150,000 per QALY
Elagolix 200 mg twice daily *short-run**	$2,900	$5,800	$8,400
Elagolix 200 mg twice daily *long-run*	$4,700	$8,800	$12,800

*Represents 6 months duration, as seen in the trials
QALY: Quality-Adjusted Life Year
All prices rounded to the nearest $100

Summary and Comment

The base case findings from our analysis suggest that the use of elagolix in endometriosis provides clinical benefit in terms of gains in health-related quality of life. This translated into cost-effectiveness estimates that were under the upper bound of commonly-cited cost-effectiveness threshold of $150,000 per QALY gained in the selected endometriosis cohort under the assumptions used in this analysis.

Costs per QALY gained versus no active treatment were approximately $126,800 and $81,000 for short-run and long-run time-horizons, respectively. The results were robust through one-way and probabilistic sensitivity analyses given the parameter uncertainties. Although somewhat sensitive to definition of treatment response, the perspective of the analysis, and other model inputs, cost-effectiveness estimates remained less than $150,000 per QALY gained.

Several important limitations surrounded our analysis. Note the unavailability of high quality long-run clinical evidence on response and discontinuation, the challenges associated with combining primary outcomes (dysmenorrhea and nonmenstrual pelvic pain) into a single combined response, and the derivation of pain scores through United Kingdom health utilities. In addition, given the FDA's approval of the higher dose of elagolix for a six-month treatment duration, the length of a treatment course in typical clinical practice is currently unknown. Perhaps most importantly, we were not able to model elagolix's costs and effects in comparison to alternative treatments due to trial population and outcome measurement differences. The calculus of elagolix's potential cost-effectiveness may differ markedly relative to an active comparator with costs, benefits, and risks of its own. These, and other critical limitations, are discussed in further detail in Section 4 of the report.

The findings of our analysis suggest that elagolix provides marginal increases in quality-adjusted survival over no active treatment. With the evidence available at this time, the estimated cost-effectiveness of elagolix 200 mg twice daily falls within the range of $50,000 to $150,000 per QALY gained.

Potential Other Benefits and Contextual Considerations

Our reviews seek to provide information on 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 elements are listed in the tables below.

Potential Other Benefits

Table ES12. Potential Other Benefits

Potential Other Benefits	Description
This intervention offers reduced complexity that will significantly improve patient outcomes.	Elagolix is an oral formulation, which may reduce healthcare complexity for women compared to GnRH agonists that are delivered via nasal spray or in-office intramuscular injections, or who are considering the potential for complications and time to recover from surgery. However, once or twice daily dosing of elagolix may lead to increased medical non-compliance.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.	If the cost of treatment is significant, those with limited financial resources may find it difficult to afford treatment. Lack of access to high quality, specialized endometrial care may also affect diagnosis and overall management of the disease.
This intervention will significantly reduce caregiver or broader family burden.	Unclear, but elagolix may improve quality of life including productivity at work and home. This may indirectly lower the burden of care provided by others to the patient or her family, especially household children.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.	Elagolix is the first GnRH antagonist to receive FDA approval for women with symptomatic endometriosis, presenting an alternative option to women who do not find relief or suffer severe side effects from other regimens. In contrast to GnRH agonists, side effects from elagolix may be more rapidly reversed and the “flare” or surge in hormones that leuprorelin acetate causes in the first few weeks of treatment may be avoided.
This intervention will have a significant impact on improving return to work and/or overall productivity.	Reducing healthcare complexity and alleviating endometriosis-related pain may improve productivity. Frequent doctor’s office visits in search of symptom relief, in combination with debilitating pain, can necessitate spending significant time away from school or work.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.	Patients expressed interest in new therapies but did not view elagolix as a game changing therapy. Some who feel that excisional surgery is underutilized expressed concern that elagolix may result in delaying surgery.

Contextual Considerations

Table ES13. Contextual Considerations

Contextual Consideration	Description
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.	Moderate-to-severe endometriosis-related pain can have a severe impact on quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.	Endometriosis has no known cure. Although it presents differently in individual patients, the disease can have a high burden of illness, particularly during a patient's reproductive years.
This intervention is the first to offer any improvement for patients with this condition.	Elagolix represents the first new treatment for endometriosis in over a decade, however patients do not view elagolix as a game changing therapy.
Compared to "the comparator", there is significant uncertainty about the long-term risk of serious side effects of this intervention.	It is unclear whether adding hormone replacement therapy to protect against bone mineral loss will increase the safety of elagolix and allow for long-term treatment with the drug.
Compared to "the comparator", there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.	It is unclear whether the comparative benefits of elagolix seen with use through six months will persist with long-term use.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.	Patients expressed a concern that industry interests have led to a focus on medical treatments in guideline recommendations, causing surgical treatment to be viewed in a more unfavorable light than they believe true.

Value-Based Benchmark Prices

Value-based benchmark prices for elagolix are presented in Table ES14. As mentioned previously, the 200 mg twice-daily dose of elagolix is FDA-approved for a six-month treatment duration only; while the eventual duration of use of elagolix in typical practice remains unknown, we nevertheless present value-based benchmarks for both the short-run and long-run time horizons below to illustrate the range of discounts from WAC that may be required.

Table ES14. Value-Based Benchmark Prices for Elagolix

	Annual WAC	Annual Price to Achieve $100,000 per QALY Threshold	Annual Price to Achieve $150,000 per QALY Threshold	Discount/ Price Premium 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%

*Represent 6 months duration, as seen in the trials
QALY: Quality-adjusted life year
All threshold prices rounded to the nearest $100
"+" indicates price premium

Potential Budget Impact

We used the results from the cost-effectiveness model to estimate the potential total budgetary impact of elagolix in place of no active treatment (non-specific rescue analgesics). We used the placeholder price of elagolix as in the cost-effectiveness analyses, and the three threshold prices in our estimates of potential budget impact. All costs were undiscounted and estimated over a five-year time horizon.

The candidate populations eligible for treatment with elagolix comprised of women in the United states between 18 and 49 years of age, diagnosed with moderate-to-severe endometriosis-related pain. We applied the estimated prevalence (6.1%) of diagnosed endometriosis to women in the 18 to 49-year age-group in the U.S, only excluding those endometriosis patients who had undergone a hysterectomy (29.2%). We assumed that women with "extremely bothersome" symptoms of dysmenorrhea and/or nonmenstrual pelvic pain represented those with moderate-to-severe endometriosis-related pain. Women with dysmenorrhea represented the higher percentage with "extremely bothersome" symptoms between dysmenorrhea and non-menstrual pelvic pain based on a cross-section survey conducted in the US in 2012.[2] Assuming this higher percentage to represent those with moderate-to-severe endometriosis-related pain, we applied this estimate to adult pre-menopausal women in the U.S (from 2018 estimated to 2022 projected population)[40] diagnosed with endometriosis who had not undergone a hysterectomy. This resulted in a target population prevalence of approximately 1.3 million patients, or approximately 270,000 patients each year over five years.

The per-patient annual budget impact using elagolix in place of no active treatment was approximately $6,800 at its WAC ($10,138 per year) and approximately $4,800 at its assumed net

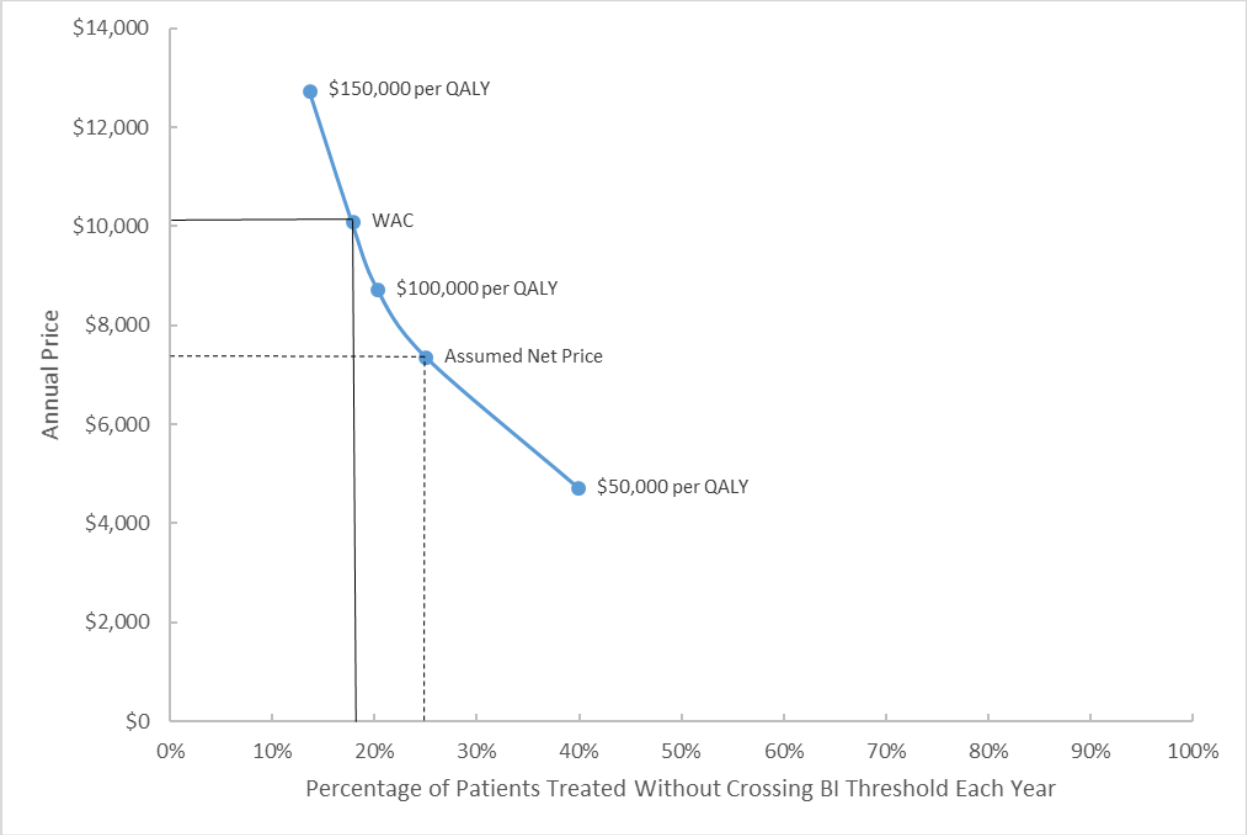
price ($7,400 per year). This estimate at the per-patient level ranged from approximately $8,800 at the price ($12,800 per year) to achieve the $150,000 per QALY threshold to approximately $3,000 at the price ($4,700 per year) to achieve the $50,000 per QALY threshold (Table ES15). The annual budget impact of treating the entire eligible population at elagolix's WAC and assumed net price were estimated at approximately $5.2 billion and $3.7 billion, respectively. At the WAC and assumed net price, only 18% and 25% of the eligible population cohort could be treated each year before the budget exceeded the ICER annual budget impact threshold of $915 million (Figure ES2).

Table ES15. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon when Treating Moderate-to-Severe Endometriosis-Related Pain

	Average Annual Per Patient Budget Impact				
	WAC	Assumed Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Elagolix 200 mg Twice Daily	$8,542	$6,605	$10,620	$7,711	$4,801
No Active Treatment	$1,789				
Difference	$6,753	$4,817	$8,832	$5,922	$3,013

WAC: Wholesale Acquisition Cost
QALY: Quality-Adjusted Life Year

Figure ES2. Potential Budget Impact Scenarios at Different Prices of Elagolix to Treat Adult Premenopausal Women Diagnosed with Moderate-To-Severe Endometriosis-Related Pain



BI: Budget Impact

Access and Affordability

At the July 12th public meeting, there was general agreement that, despite the availability of alternative treatments for the medical management of moderate-to-severe endometriosis pain, the potential patient population that can be treated with elagolix remains large. Additionally, since elagolix is an oral agent, patients and clinicians may prefer it over other treatments such as GnRH agonists. There can be a rapid return of endometriosis symptoms once elagolix has been discontinued; therefore, if benefit is seen early on in treatment with elagolix, patients and clinicians may wish to use this drug long-term, thus leading to higher treatment costs.

Our estimates of potential budget impact of elagolix indicated that at its net price, assuming a 27% discount from WAC, only 25% of all eligible patients could be treated before costs exceeded ICER's potential budget impact threshold of $915 million per year. Given that optimal clinical uptake at current estimated discount prices would lead to 5-year costs far in excess of this threshold, ICER is issuing an Access and Affordability Alert at this time. 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.

Summary of the Votes and Considerations for Policy

At the July 12, 2018 meeting, the New England CEPAC panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of elagolix for treating patients with endometriosis. Following the evidence presentation and public comments, the NE CEPAC panel voted on key questions concerning the comparative clinical effectiveness, potential other benefits and contextual considerations related to elagolix. The NE CEPAC panel did not deliberate or vote on the value of elagolix because the manufacturer had not yet announced the launch price, and ICER's economic evaluation had therefore used a placeholder price. The vote tallies are summarized below, and a full summary of the discussion is included in Section 8.2 of the full report.

1) Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by no treatment?

Yes: 1 votes	**No: 11 votes**

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?

Yes: 0 votes	**No: 12 votes**

3) Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by hormonal contraceptive, depot medroxyprogesterone?

Yes: 0 votes	**No: 12 votes**

4) When compared to no treatment, does elagolix offer one or more of the following "potential other benefits"? (select all that apply)

# of Votes	Potential Other Benefits
0/12	This intervention offers reduced complexity that will significantly improve patient outcomes.
4/12	This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
4/12	This intervention will significantly reduce caregiver or broader family burden.
9/12	This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
5/12	This intervention will have a significant impact on improving patient's ability to return to work and/or their overall productivity.
6/12	Other important benefits.

5) Are any of the following contextual consideration important in assessing long-term value for money? (select all that apply)

# of Votes	Contextual Considerations
10/12	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
8/12	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
1/12	This intervention is the first to offer any improvement for patients with this condition.
9/12	Compared to no treatment, there is significant uncertainty about longterm risk of serious side effects.
9/12	Compared to no treatment, there is significant uncertainty about the magnitude or durability of long-term benefits.
7/12	Other important contextual considerations

Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on elagolix in treating patients with endometriosis to policy and practice. The roundtable discussion was facilitated by Dr. Dan Ollendorf, PhD, Chief Scientific Officer of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below. A more detailed description of each recommendation is included in section 8.3 of the main report.

Payers

(1) ***Elagolix has known short-term side effects and no long-term comparative safety and efficacy data in relation to several other well-established treatment options for endometriosis. It is therefore reasonable for insurers to develop prior authorization criteria for elagolix to ensure prudent use.***

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 are discussed below.

Potential patient eligibility criteria:

- Premenopausal women with symptomatic endometriosis who have had inadequate symptom relief after at least three months of first-line therapy with nonsteroidal anti-inflammatory meds (NSAIDs) and hormonal contraceptives. If adequate improvement in symptoms is not seen after a trial of these medicines, then consideration of second-line therapies or possibly surgical intervention would be appropriate.
- The lack of comparative data favoring the safety or effectiveness of elagolix over leuprorelin acetate suggests that insurers may explore the option of requiring a trial of leuprorelin acetate prior to coverage for elagolix. For insurers contemplating this step therapy coverage approach, several important factors should be considered, including the time needed for reversibility of side effects, the mode of administration, and the duration of action.

Potential provider criteria: Elagolix may be covered only if prescribed by a specialist clinician with formal training in obstetrics/gynecology or reproductive endocrinology. However, it was acknowledged that in some regions, subspecialists with this level of training may not be available. Insurers may consider limiting provider prescribing of elagolix to subspecialists but should consider the potential impact on access for some patients. One

option may be to require generalist prescribers of elagolix to seek consultation from subspecialists through telehealth or other methods.

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. Insurers may require that coverage beyond that time requires clinician attestation of clinical improvement and documentation that lipids and bone mineral density are being monitored.

(2) 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.

(3) 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.

(4) Manufacturers and researchers in the area of endometriosis owe patients, clinicians, and insurers better information on the long-term comparative clinical effectiveness and value of innovative new therapies. For elagolix, they should take action to ensure that future studies are developed to directly compare elagolix with other treatment options using standardized research protocols that focus on outcomes that reflect what matters most to patients.

(5) 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.

(6) Professional societies should take steps to address and minimize potential financial and professional conflicts of interest; and to collaborate with patients and methodological experts in new efforts to develop comprehensive and unbiased guidelines and educational outreach for patients with endometriosis.

(7) Regulators have an important role to play in how new therapeutics enter clinical practice and therefore 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.

1. Introduction

1.1 Background

Endometriosis is a chronic gynecological condition characterized by the attachment and proliferation of endometrial-like tissue outside of the uterus.[1] Though most women have retrograde menstruation that can explain endometrial-like tissue outside of the uterus, only a few develop endometriosis, pointing to other contributing factors such as the body's immune response.[1] Common symptoms of endometriosis include painful menstrual periods, nonmenstrual pelvic pain, pain during intercourse (dyspareunia) and infertility.[1] The nature of the pain can vary among affected women and occur unpredictably within an individual: it can be continuous or intermittent; it can feel sharp, dull, burning or throbbing; be exacerbated or unrelated to activity; and cause bowel or bladder symptoms such as nausea, urgency, and bloating. Pain associated with endometriosis can decrease a patient's quality of life by increasing depressive symptoms, reducing sexual satisfaction, and disrupting personal relations.[5,6] It can also affect ability to work,[41] and results in estimated health care costs of over $10,000 per patient per year in the United States and over $15,000 per patient per year in lost work productivity.[7,8]

Endometriosis affects 6-10% of women of reproductive age, with peak prevalence between 25 to 35 years of age and is estimated to affect four to ten million women in the United States.[2-4] Endometriosis is the most common cause of chronic pelvic pain.[42] It is a cause of pelvic pain in up to 60% of teenage girls and women, and 50% of women with infertility.[4] Physical examination findings, blood tests and non-invasive imaging can help exclude other causes of pelvic pain, but direct visualization at surgery is the definitive way to diagnose and stage endometriosis. For this reason, the diagnosis of endometriosis is often delayed and contributes to the burden of pain, infertility, and quality of life.[5]

A range of pharmacologic and surgical treatments are available and have been shown to decrease the severity and frequency of patient symptoms, but none appear to offer a cure or long-term relief.[9,10] Moreover, the relationship between endometriosis and infertility is poorly understood and pharmacologic treatments have not been shown to improve rates of pregnancy.[43] Initial treatment of endometriosis often includes a trial of nonsteroidal anti-inflammatory drugs and hormonal contraceptive therapy.[11] Hormonal therapies whether delivered by oral, depot injection, implants or intrauterine devices have shown similar benefits in terms of controlling pain symptoms, although only some are FDA-approved for endometriosis. One type of hormonal therapy, gonadotropin-releasing hormone (GnRH) agonists, is not considered first-line therapy and is not recommended for adolescents because of concerns about long-term bone loss.[12] Aromatase

inhibitors, most commonly used as a hormonal treatment for women with breast cancer to prevent recurrence, has also been shown to improve symptoms in women with endometriosis.[44]

Surgery is another common treatment option for women with symptomatic endometriosis and may occur at the time of a diagnostic laparoscopy or after an insufficient response to medical therapy.[13,14] For those with persistent symptoms, pain management may require repeated courses of hormonal or surgical treatments until menopause,[45] the time at which endometriosis symptoms subside in most women, and chronic pain due to endometriosis is a cause of chronic opioid use with its attendant risks.[46] Surgical treatment is also considered for infertility associated with endometriosis.[15] Definitive therapy with surgical removal of the uterus and ovaries along with excision of extra-uterine disease is reserved for women with symptoms that are not controlled with other treatments and who have completed childbearing.

Given the limitations of currently available treatments, there is considerable interest in new therapeutic options to treat patients with moderate-to-severe pain due to endometriosis unresponsive to first line therapy with NSAIDs and hormonal contraception. A new agent, elagolix (Orilissa™, AbbVie) was approved by the FDA for the management of moderate-to-severe pain associated with endometriosis on July 23, 2018.[16]

Gonadotropin-Releasing Hormone (GnRH) Therapies for Endometriosis

The pituitary gland produces gonadotropin-releasing hormone that regulates the primary female hormones, luteinizing hormone (LH) and follicle stimulating hormone (FSH). GnRH agonists work by mimicking the action of the naturally occurring hormone and binding to the GnRH receptor. This results in GnRH agonists initially stimulating the pituitary gland to release the hormones LH and FSH and can worsen symptoms of endometriosis during the first 10 to 14 days of treatment. As a result, when starting treatment with GnRH agonists, oral contraceptive pill (OCP) or a progestin, commonly norethindrone, are given to prevent worsening of symptoms and to minimize side effects. With prolonged, continuous exposure to these agents, pituitary secretion of hormones is decreased due to down-regulation of the GnRH receptor and pituitary desensitization. The decrease in these hormone levels leads to full suppression of production of estradiol and progesterone by the ovaries.

In contrast, elagolix, a short-acting, nonpeptide, GnRH antagonist rapidly suppresses the pituitary-ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production that varies from partial to full suppression depending on the frequency and dose given.[17,18] By not producing the initial surge in LH and FSH associated with GnRH agonists, elagolix does not result in an initial increase in symptoms and the need to treat with hormonal contraceptives. Moreover, GnRH agonists must be administered by injection or intranasally, whereas elagolix is an oral medication.

The low estrogen state induced by GnRH agonists and antagonists leads to the main side effects including hot flashes, vaginal dryness, decreased libido, mood swing and headache. The potential for elagolix to produce partial suppression at lower doses may decrease endometriosis-related pain while minimizing the hypoestrogenic side effects that limit long-term treatment with agents that fully suppress ovarian hormones. Because hormonal agents are associated with a return of endometriosis-related symptoms after discontinuation, the need for prolonged use of GnRH agonists or antagonists that fully suppress ovarian hormones can lead to decreased bone density (osteoporosis). Therefore, GnRH agonists are approved for only up to six months of continuous use. However, GnRH agonists have been used long-term with the addition of hormonal contraceptives (i.e., "add-back" therapy) to decrease symptoms and prevent bone loss.[47] No studies have been reported using add-back therapy for elagolix. Although it may be expected that such therapy would be considered for long-term use of higher doses of elagolix, the FDA prescribing information urges caution in using estrogen-containing hormonal contraception because it may decrease the efficacy of elagolix.[16]

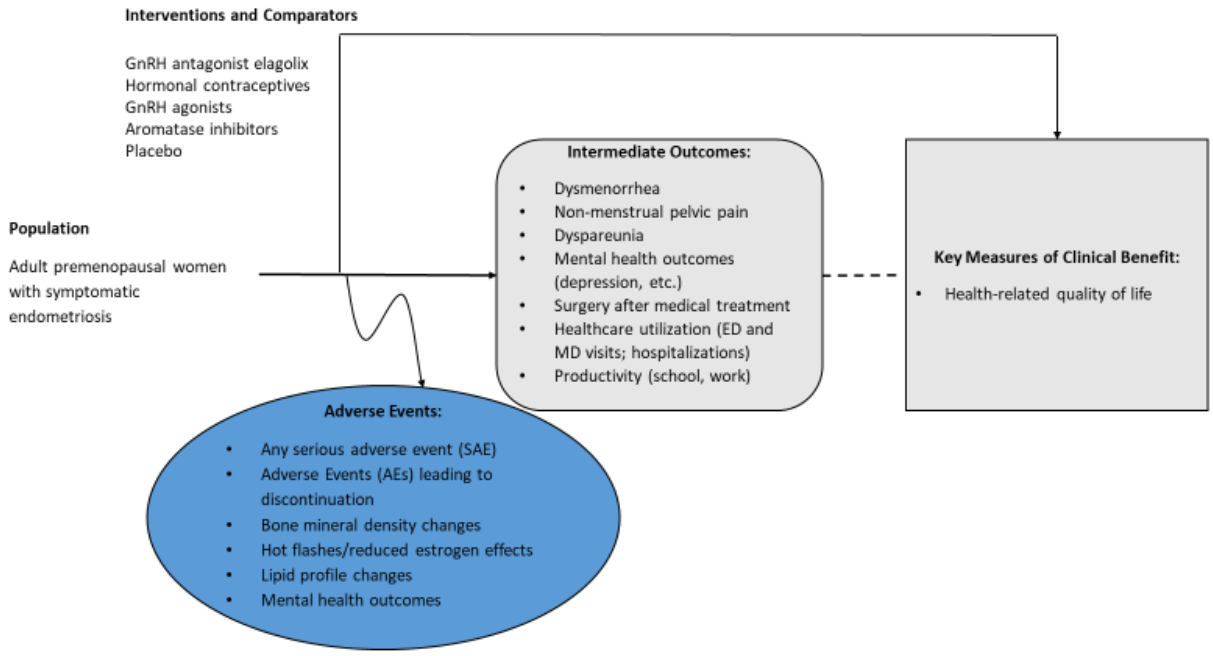
1.2 Scope of the Assessment

This review evaluated the comparative clinical effectiveness of the GnRH antagonist, elagolix, for the treatment of adult premenopausal women with symptomatic endometriosis. Evidence was collected from available randomized controlled trials, non-randomized clinical trials, comparative observational studies, as well as high-quality systematic reviews. We limited our review to those studies that captured the outcomes of interest. We did not restrict studies according to number of patients or study setting; however, we limited our review to those that measured the outcomes of interest of at least three months. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/). We sought head-to-head studies of elagolix and comparators to evaluate the feasibility of a network meta-analyses of selected outcomes.

Analytic Framework

The general analytic framework for assessment of therapies for endometriosis is depicted in Figure 1.1.

Figure 1.1. Analytic Framework: Therapies for Endometriosis



The diagram begins with the population of interest on the left. Actions, such as treatment, are depicted with solid arrows which link the population to outcomes. For example, a treatment may be associated with specific health outcomes. Outcomes are listed in the shaded boxes; those within the rounded boxes are intermediate outcomes (e.g., reduction in nonmenstrual pelvic pain), and those within the squared-off boxes are key measures of benefit (e.g., health-related quality of life). The key measures of benefit are linked to intermediate outcomes via a dashed line, as the relationship between these two types of outcomes may not always be validated. Curved arrows lead to the adverse events of treatment which are listed within the blue ellipse.[48]

Populations

The population of focus for this review is adult premenopausal women with symptomatic endometriosis.

Interventions

The intervention of interest for this review is the GnRH antagonist elagolix.

Comparators

We examined studies comparing elagolix to placebo or other types of active medications used to treat endometriosis. Active treatments we considered included GnRH agonists (with or without low-dose add-back therapy), hormonal contraceptives, and aromatase inhibitors. Wherever possible, we evaluated head-to-head trials of the interventions. If suitable data were available, the review sought to include head-to-head comparisons through methods such as network meta-analysis.

Outcomes

This review examined key clinical outcomes associated with endometriosis. The outcomes of interest and key harms are described in the table below. We engaged with patient groups and clinical experts to ascertain which outcomes are of greatest importance to patients and sought patient-reported outcomes or other evidence sources to enrich the available data. Discussion with patients, patient groups, and clinicians indicated that clinical trials may lack robust information on the broader impact that endometriosis can have on the lives of women and their families.

Outcomes and key harms of interest from clinical trials included:

Table 1.1. Key Outcomes and Harms

Outcomes	Key Harms
Dysmenorrhea	Reduced bone mineral density
Nonmenstrual pelvic pain	Lipid profile changes
Dyspareunia	Hot flashes
Mental health (depression, etc.)	Headache
Reduced use of analgesics	Insomnia
Productivity	Amenorrhea
Health care utilization	Night sweats
Quality of life	Arthralgia
Surgery after medical treatment	Congenital malformations
	Vaginal dryness
	Decreased libido
	Mental health outcomes

Although infertility can be an issue of great importance to women with endometriosis, we limited our review to outcomes related to pain symptoms and their physical and psychosocial impact. While the ability to conceive a child is extremely important, the primary indication for elagolix, according to the manufacturer, is to reduce endometriosis-related pain symptoms. Though women were supposed to use two forms of birth control, we summarize pregnancy outcomes as an unintended consequence and review whether any of these pregnancies showed evidence of potential teratogenic effects associated with elagolix treatment.

Evidence tables were developed for each selected study and results were summarized in a qualitative fashion. If available data permitted, we sought to perform meta-analysis to quantitatively summarize outcomes for the therapies of interest, and network meta-analysis to combine direct and indirect evidence of effectiveness.

Timing

Evidence on intervention effectiveness and harms was derived from studies of at least three-month duration.

Settings

All relevant settings were considered, with a focus on outpatient settings in the United States.

1.3 Definitions

Dysmenorrhea: pain or cramps that occur during the menstrual period. Symptoms can begin right before or during the time that menstruation or bleeding occurs. The pain is usually in the pelvis or lower abdomen.

Dyspareunia: refers to pain in the genital or pelvic region that is associated with a woman having sexual intercourse.

Biberoglu and Behrman (B&B) scale: The B&B assesses function and quality of life and is not a pain scale. It consists of three patient-reported symptoms (dysmenorrhea, dyspareunia, and pelvic pain not related to menses) and two signs assessed during pelvic examination (pelvic tenderness and induration). Each symptom is graded on a four-point scale from 0 to 3, with higher numbers indicating more severe symptoms (0=none, 1=mild, 2=moderate, 3=severe). A total pelvic pain scale sums the three symptoms questions and is classified as none (0), mild (1-3), moderate (4-6) and severe (7-9). The B&B has undergone a number of modifications over time including changes to permit daily collection as part of a symptom diary.[22,25,27]

Composite Pelvic Signs and Symptoms Score (CPSSS): The CPSSS is derived from all five items in the B&B scale.[27] It is a validated instrument used to assess the signs and symptoms of endometriosis. The instrument includes five components, which address dysmenorrhea, dyspareunia, nonmenstrual pelvic pain, pelvic tenderness, and pelvic induration. Each component of the CPSSS is scored on a scale of 0 to 3 (0=None; 1=mild; 2=moderate; 3=severe). The total CPSSS has a maximum possible value of 15, with lower scores indicating fewer signs and symptoms of endometriosis.[23,24] Severity is rated as none (0), mild (1-2), moderate (3-5), severe (6-10) and very severe (11-15).

Endometriosis Health Profile (EHP): The EHP is a disease-specific instrument designed to assess quality of life in women with endometriosis. The self-administered questionnaire evaluates five core dimensions, which include pain, control and powerlessness, emotional well-being, social support, and self-image. Six modular parts were also developed to measure sexual intercourse, work, relationship with children, feelings about the medical profession, treatment, and infertility. The EHP was initially developed as a 30-item questionnaire (EHP-30); a shorter version, the EHP-5 was also developed to include 11 questions in the same five core dimensions. Items on both the core and modular questionnaires are rated on a four-point scale (never=0, rarely=1, sometimes=2, often=3, always=4). Scores are standardized on a scale of 0-100, with lower scores indicating better quality of life. Both the EHP-5 and EHP-30 have been validated.[49]

Patient Global Impression of Change (PGIC): A patient reported outcome (PRO) was created to measure a patient's perspective of treatment efficacy in clinical trials.[50] The PGIC, a seven-point scale reflecting patients' rating of overall improvement, ranges from 1 ("very much improved") to 7 ("very much worse"). Available responses include "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse" or "very much worse".[50]

1.4 Insights Gained from Discussions with Patients and Patient Groups

In developing and executing this report, we received valuable input from individual patients and patient advocacy groups throughout the scoping and evidence development process. Below we summarize the key insights derived from this input.

Despite being a common cause of chronic pelvic pain, the diagnosis of endometriosis is often delayed. This may occur for a variety of reasons, but the result is frustration on the part of patients and a perception that health care providers are not taking their complaints seriously. Because episodic pelvic pain is a common symptom in adolescent women associated with the onset of menses, chronic or severe symptoms may be misattributed to normal menstrual periods. When treatment is recommended it often will start with non-specific pain medications such as non-steroidal anti-inflammatory drugs (NSAIDs). The use of hormonal contraceptives may be started at the same time as NSAIDs or added if initial therapy isn't helping. It may take several menstrual cycles to assess whether hormonal contraceptives are helping or not. If not, the therapy may be changed from cyclical to continuous hormonal contraceptives or the use of progesterone only hormones delivered by a variety of means. After potentially many months of different therapies, women who continue to be symptomatic may then undergo a more thorough evaluation for other causes of chronic pelvic pain. This may further delay definitive diagnosis because there are no blood tests or imaging studies (including ultrasounds and magnetic resonance imaging [MRI]) that can reliably diagnose endometriosis. The one exception is that imaging studies can detect ovarian cysts (endometriomas) and establish a diagnosis of endometriosis, but not all women with endometriosis have an endometrioma.[51] Since definitive diagnosis requires laparoscopic surgery, an

invasive procedure, the decision to operate may be influenced by perceptions of severity due to the subjective nature of pain symptoms and the young age of the patients. The net effect is that the average interval between onset of pain and surgical diagnosis can be six to ten years.[19,20]

Even after a definitive diagnosis is made, patients and patient advocacy groups highlight the deficiencies with currently available treatments for endometriosis. The lack of therapies that provide long-term relief with minimal side effects or risks are viewed as pointing to insufficient knowledge of what causes endometriosis to develop in the first place and then to persist over time despite hormonal therapies that can fully suppress the production of ovarian hormones. Though non-opioid drugs and hormonal contraceptive therapies have fewer side effects, they have been found to be ineffective in many women.[21] Therapies like GnRH agonists and potentially GnRH antagonists like elagolix may be considered second line therapies in guideline recommendations. It is also recognized that lower fertility rates in women with endometriosis have not improved with hormonal therapies.

Some patients and patient advocacy groups perceive that use of hormonal therapies results in delaying more effective surgical interventions. Though there are strong advocates for greater use of surgery and more aggressive procedures to treat visually identified endometrial-like tissue, available evidence does not clearly demonstrate the superiority of this approach over less aggressive procedures or medical treatments. Aggressive surgical procedures are believed to result in longer symptom control and less symptom recurrence, but surgery has not been demonstrated to result in a cure for endometriosis. This is highlighted by studies showing that adding hormonal therapy after surgery results in longer pain control than surgery alone.[21]

A recurring theme has been that the common outcome measures used in clinical literature may not adequately capture the impact of endometriosis on overall quality of life including relationships, work and family issues. This may relate in part to a perception that endometriosis is a subjectively worse version of menstrual symptoms. As a result, patients and patient advocacy groups suggest that symptoms of endometriosis are more impactful on diminished quality of life, both physically and emotionally, than people realize. Stakeholders indicated that endometriosis can be a serious and disabling condition that affects women throughout their reproductive years.

Finally, patients and patient advocacy groups emphasized the limited evidence and lack of research being done given the prevalence, severity and impact of endometriosis among women of reproductive age. They note that the last FDA approved medicines for endometriosis, GnRH agonists, were approved over 20 years ago and that other, newer agents such as aromatase inhibitors, have not been adequately studied.

1.5. Potential Cost-Saving Measures in Endometriosis

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 headroom in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/final-vaf-2017-2019/). During stakeholder engagement and public comment periods, ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) currently used for people with endometriosis that could be reduced, eliminated, or made more efficient.

Patient advocates felt that increased awareness of endometriosis and it symptoms could lead to more rapid diagnosis. It is possible that preventing the years of symptoms before an accurate diagnosis is made could decrease the cost of care. We did not identify any published recommendations from initiatives such as the Choosing Wisely® campaign that are relevant to this clinical area.

2. Summary of Coverage Policies and Clinical Guidelines

2.1 Coverage Policies

We analyzed insurance coverage for both on and off label treatment options for patients with endometriosis in 13 silver-tiered insurance plans on individual marketplaces across New England. A complete listing of plans surveyed, and key formulary designs, are included in Appendix B.

In general, commercial carriers in New England do not follow any specific protocols for treating patients with endometriosis pharmacologically. All plans offer coverage for at least one hormonal contraceptive option without drug management due to requirements by the Affordable Care Act;[52] and all plans surveyed cover two out of three aromatase inhibitors, usually on the lowest tiers for cost sharing with no prior authorization. The three aromatase inhibitors became available as generics in 2010.[53]

All New England commercial plans cover at least one GnRH agonist, although nafarelin is most likely to be covered without prior authorization. Leuprorelin acetate is covered by two-thirds of the plans surveyed but requires prior authorization and reauthorization of treatment every six months in nearly all plans. In their prior authorization, it is common for plans to require diagnosis from a specialist to prescribe GnRH agonists for patients with endometriosis. While they may cover GnRH agonists for other approved indications, several plans also explicitly exclude coverage of GnRH agonists for patients with endometriosis. Certain plans have lifetime maximums for treatment with a GnRH agonist of 12 months, however, they can be waived by a special provider appeal. An overview of common policies is included in the table below.

Table 2.1. Coverage Policies for Reviewed Treatments for Endometriosis

	Percent of Commercial Insurance Plans Covering	Prior Authorization Required	Diagnosis or Pre-Treatment by a Specialist	Initial Treatment Approval Duration ≤ 6 Months
GnRH Inhibitors				
Leuprorelin acetate (Lupron)	69%	89%	56%	89%
Goserelin (Zoladex)	54%	86%	43%	57%
Nafarelin (Synarel)	85%	45%	27%	27%
Aromatase Inhibitors				
Letrozole (Femara)	77%	0%	0%	0%
Exemestane (Aromasin)	92%	23%	0%	0%
Anastrozole (Arimidex)	92%	0%	0%	0%

2.2 Clinical Guidelines & Consensus Statements

Treatment recommendations have been developed by the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Reproductive Medicine.[9,10] The ACOG guideline for the management of endometriosis was published in 2010. It found good and consistent evidence that medical suppressive therapy and surgical treatment improve pain symptoms, but that pain recurrence was common after medication discontinuation or post-surgery. Evidence supports surgical management but not medical suppressive therapy for endometriosis-related infertility and endometriomas. Excision of an endometrioma is superior to simple drainage and ablation of the cyst wall. Use of add-back hormonal therapy for patients responding to and planning continued GnRH agonist therapy is recommended. Add-back therapy can minimize bone mineral loss and provides symptomatic relief without reducing the efficacy of pain relief. Combined oral contraceptives and oral norethindrone or depo-medroxyprogesterone acetate are effective compared with placebo and are considered equivalent to more costly therapies, including GnRH agonists. An updated ACOG guideline is under review.

The American Society for Reproductive Medicine (ASRM) updated its treatment recommendations in 2014. It highlighted viewing the treatment of endometriosis as reflecting the chronic nature of this disease requiring a lifelong management plan for affected women. A key aspect of this is an emphasis on maximizing the use of medical treatment and avoiding repeated surgical procedures. In addition to pelvic symptoms of dysmenorrhea, nonmenstrual pain, and dyspareunia, endometriosis can have gastrointestinal, urinary, musculoskeletal, and psychological symptoms. This range of symptoms requires efforts to identify or exclude other conditions that can mimic these symptoms. As such, definitive diagnosis via laparoscopic surgery remains essential, with the ability to treat visible endometriosis at that time. The guideline identifies several effective medical and surgical treatments for symptoms due to endometriosis, and recommends medical therapy following surgical treatment due to longer symptom relief than with surgery alone. Definitive surgical treatment with removal of the uterus and ovaries (total hysterectomy and bilateral salpingo-oophorectomy) should be considered only for women with disabling symptoms who have completed childbearing and have failed to respond to multiple alternative treatments. The ASRM identified the need for further studies to compare outcomes of medical and surgical treatments of endometriosis.

In 2013, the World Endometriosis Society put forward their *Consensus on current management of endometriosis*.[54] The consensus statement process was not the same as formal guideline development, however it was the first time that experts from around the world convened to evaluate evidence and form consensus on the management of endometriosis. The consensus statement was published in *Human Reproduction* in February 2013. They agreed that endometriosis ought to be considered a spectrum of disease, and diagnosis should not be limited to those with laparoscopic diagnosis. They agreed that diagnosis should be in a primary care setting

for those women with pelvic and abdominal pain, and/or infertility. There was consensus that patients should have a multidisciplinary team of experts trained in endometriosis at a center of expertise, including a surgeon, to tailor treatment strategies to each patient based on their severity and priorities on fertility. Importantly, the consensus statement asserts that there is strong evidence to demonstrate that laparoscopic surgical removal is an effective first line treatment for treating pain, and there is consensus to prefer excision over ablation. After surgery, they suggest that NSAIDs and OCP are effective ways to control pain and minimize recurrence after surgery. Danazol and gestrinone are not recommended. While there was no consensus, a majority voted (50-80%) that GnRH agonists and aromatase inhibitors might be considered for second line treatment, although evidence is weak.

The U.K. National Institute for Health and Care Excellence (NICE) most recently updated their guidelines for treating endometriosis in September 2017, including recommendations on diagnosis, pharmacological pain management, and surgical management.[21] The NICE guidelines were developed in conjunction with a systematic review and comparative clinical effectiveness evaluation, the results of which are summarized in Section 3. NICE's guidelines recommend diagnosing endometriosis through pelvic and abdominal examination, ultrasound or MRI, and diagnostic laparoscopy. For women with endometriosis related pain, NICE recommends a short trial of NSAIDs, followed by treatment with hormonal treatments such as oral contraceptives and progestogen. When fertility is a priority, NICE recommends direct referral to a multidisciplinary team and fertility specialist, excluding treatment with hormonal contraceptives. If pain symptoms persist, NICE recommends discussing surgical options with the patient, preferring excision over ablation, depending on the patient's priorities for her fertility and ovarian reserve. For endometriosis affecting the bowel, bladder, or ureter, NICE recommends considering GnRH agonists for three months prior to surgery, although not all GnRH agonists are approved for use in the U.K. and may need special approval. NICE presents hysterectomy and removal of ovaries as an option for women when other treatments have been unsuccessful.

3. Comparative Clinical Effectiveness

3.1 Overview

To inform our analysis of the comparative clinical effectiveness of elagolix in the management of adult premenopausal women with symptomatic endometriosis, we abstracted evidence from available clinical studies, whether in published or unpublished form (e.g., conference abstracts or presentations, FDA review documents).

As mentioned in the Background section, comparators of interest included GnRH agonists (with or without hormone replacement), hormonal contraceptives, aromatase inhibitors, and placebo. Due to key differences in study eligibility criteria, baseline characteristics of study populations, and outcome measurements, we did not attempt to compare elagolix to other hormonal therapies for endometriosis through indirect quantitative assessment. Our review focused on clinical benefits (i.e., pain relief, impaired function, mental health, productivity, healthcare utilization, surgery after medical treatment and health-related quality of life), as well as potential harms (drug-related adverse events).

3.2 Methods

Data Sources and Searches

We searched MEDLINE, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials via the Ovid platform and EMBASE directly via the EMBASE website. All search strategies were generated utilizing the Population, Intervention, Comparator, and Study Design elements described in the scope above (Section 1.2). The search strategy included a combination of indexing terms (MeSH terms in MEDLINE and EMTREE terms in EMBASE), as well as free-text terms, and are presented in Appendix A2. The date of the most recent search was February 16, 2018.

To supplement the database searches, we performed a manual check of the reference lists of included trials and pertinent systematic reviews. We also invited key stakeholders to share references germane to the scope of this project. We supplemented our review of published studies with data from conference proceedings, regulatory documents, information submitted by manufacturers, and other grey literature when the evidence met ICER standards (for more information, see http://icerreview.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

Because recent, high-quality systematic reviews of treatments for endometriosis were available, we utilized these reports to identify evidence on relevant comparators. Our primary source was the 2017 National Institute for Health and Care Excellence (NICE) review, but we also utilized a peer-reviewed systematic review published in 2017 from Becker and colleagues.[21,55]

Study Selection

After removal of duplicate citations using both online and local software tools, citations went through two levels of screening at both the abstract and full-text level. Two reviewers independently screened the titles and abstracts of all publications identified using DistillerSR (Evidence Partners, Ottawa, Canada); a third reviewer resolved disagreements. Abstracts were screened based on population, intervention, relevant outcomes and study design.

Citations accepted during abstract-level screening were reviewed as full text. The review followed the same procedures as the title/abstract screening. Reasons for exclusion were categorized according to the PICOTS elements during both title/abstract and full-text review.

Although comparators of interest were included in our literature search, they were not selected during title/abstract or full-text screening due to the availability of recent, high-quality systematic reviews of evidence on these therapies. As noted above, we used the 2017 National Institute for Health and Care Excellence (NICE) Endometriosis Guideline and the peer-reviewed publication from Becker and colleagues (2017) to identify relevant literature on GnRH agonists, hormonal contraceptives, and aromatase inhibitors.[21,55] To ensure that no studies were missed, we searched for evidence on comparator therapies published after NICE conducted their search (December 2016). As comparators have been evaluated relative to myriad therapies, many of which were out of scope or no longer commonly used in clinical practice, we focused attention primarily on placebo-controlled trials.

Data Extraction and Quality Assessment

Data were extracted directly into the Systematic Review Data Repository (SRDR™; https://srdr.ahrq.gov/). From SRDR, data were transferred into evidence tables (see Appendix E, Table E2). Elements include a description of patient populations, sample size, duration of follow-up, study design features (e.g., open-label or cross-over periods), outcome assessments (e.g., timing, definitions, and methods of assessment), results, and quality assessment for each study. The data extraction was performed in the following steps:

1. One reviewer extracted information from the full articles, and a second reviewer validated the extracted data.

2. Extracted data were reviewed for logic, and a random proportion of data were validated by a third investigator for additional quality assurance.

We used criteria employed by the US Preventive Services Task Force ([USPSTF] see Appendix E) to assess the quality of clinical trials and cohort studies, using the categories "good," "fair," or "poor."[56]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix to evaluate the level of certainty in the available evidence of a net health benefit for elagolix relative to alternative therapies for endometriosis-related pain (see Appendix E, Figure E1).[57]

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias for elagolix using the ClinicalTrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies may indicate whether there is bias in the published literature. For this review, we did not find evidence of any study completed more than two years ago that that has not subsequently been published.

Data Synthesis and Statistical Analyses

Data on relevant outcomes were summarized in evidence tables (see Appendix Table E2) and are synthesized in the text below. Due to major differences in study design, baseline characteristics of study populations, and outcomes assessed, we did not conduct quantitative direct or indirect analyses of elagolix versus any comparator.

3.3 Results

Study Selection

Our literature search identified 1,699 potentially relevant references (see Appendix Figure A1), of which five references relating to five trials of elagolix met our inclusion criteria. Two of the five studies were Phase III randomized controlled trials (RCTs); three studies were Phase II placebo- or active-controlled trials.[22-25] An additional reference reported on data from two double-blind extension studies of the phase III trials. The primary reasons for study exclusion included study populations outside of our scope (e.g., endometrial cancer, healthy women and adenomyosis), interventions not of interest and indications outside the scope of our review (e.g., use in fertility). Specifically, no additional eligible studies of GnRH agonists, hormonal contraceptives or aromatase inhibitors subsequent to the NICE literature search were identified. Additional details of the included references are described in Appendix E, and the key studies are summarized in Table 3.1.

The selected studies provided outcomes data on elagolix for at least three months duration. Four of the five key studies were placebo-controlled trials.[22,24,25] One phase II study (Tulip PETAL) included the GnRH agonist, leuprorelin acetate, as an active comparator in addition to a placebo arm; a fifth study, the phase II PETAL trial, evaluated elagolix in comparison to a hormonal therapy,

depot medroxyprogesterone acetate (DMPA-SC), without a placebo arm.[22,23] We found no studies of elagolix versus an aromatase inhibitor.

Since trials of many of the GnRH agonists and hormonal contraceptive comparators were performed years before trials of elagolix and assessed these treatments relative to other therapies that were outside of our scope (e.g., danazol), we focused on placebo-controlled studies.

Elagolix Studies

As described above, our literature search identified two Phase III trials, three Phase II trials, and two extension trials that provided outcomes data of at least three months duration.[22-25] These studies are summarized in Table 3.1 below. The first Phase III trial, EM-I, enrolled 872 women at 151 clinical sites in North America.[24] An identically designed Phase III RCT, EM-II, enrolled 817 women at 187 sites in North America, South America, Europe, Africa and Australia.[24] In both studies, patients with a surgical diagnosis of endometriosis within 10 years of screening and moderate-to-severe endometriosis-associated pain were randomized to receive elagolix 150 mg daily, elagolix 200 mg twice daily, or placebo for 6 months after a wash-out from current hormonal therapies and a 75-day screening period to allow for physical evaluations and 45 days of reporting daily pain assessments in electronic diaries.[24]

Two extension trials, EM-III and EM-IV, were also included in our review. In these studies, women receiving elagolix in the Phase III trials received an additional six months of blinded treatment (12 months total) and were followed for up to 12 months posttreatment.[26] Women who were initially randomized to placebo in the Phase III EM-I and EM-II studies were switched to elagolix in the extension studies but data from these patients are not yet reported.

Two of the three Phase II studies in our set included placebo comparisons. The Lilac PETAL trial from Diamond and colleagues randomized 155 women with laparoscopically-confirmed (within eight years of screening) symptomatic endometriosis to elagolix 150 mg daily, elagolix 250 mg daily, or placebo for 12 weeks after an eight-week screening and four-week lead-in placebo period. After the 12-week treatment period, patients in the placebo group were re-randomized to elagolix for an additional 12 weeks of treatment.[25]

The Tulip PETAL trial, which was conducted at 27 centers in Central Eastern Europe (Bulgaria, Hungary, Poland, Romania, Russia, and Ukraine), also reassigned patients to different treatment arms after 12 weeks of treatment.[22] In this study, women (n=174) ages 18-45 years with a laparoscopically confirmed diagnosis within 60 weeks of screening and symptomatic endometriosis were initially randomized to receive elagolix 150 mg daily, elagolix 250 mg daily, placebo, or leuprorelin acetate one-month depot 3.75 mg intramuscularly for 12 weeks. After 12 weeks, patients in the placebo and leuprorelin acetate groups randomly crossed over to each of the

elagolix groups and were treated for an additional 12 weeks; patients who started on elagolix maintained their original assignment.[22]

The third Phase II trial of interest, the PETAL trial, was a multicenter, double-blind, active-controlled trial in which 252 patients were randomized 1:1:1 to elagolix 150 mg once daily, elagolix 75 mg twice daily, or depot medroxyprogesterone (DMPA-SC) 104 mg/0.65 mL (subcutaneous injection at weeks one and twelve).[23] Women ages 18-49 years with a laparoscopically documented diagnosis within seven years of screening and endometriosis-associated pain were treated for 24 weeks across 78 US centers and followed for an additional 24 weeks.[23]

Table 3.1. Elagolix Trials

Key Trials	Treatment and F/U Duration	Treatment Groups	Patient Characteristics	Primary Outcome
EM-I, 2017[24,26] Phase III Parallel-arm RCT	6-month treatment period + 6 months of treatment in extension study; 12 months post-treatment follow-up	Placebo Elagolix 150 QD Elagolix 200 BID	N=872 Median age: 31 Age range: 18-48 Caucasian: 87% BMI (kg/m^2): 28	Clinical Responders (%) defined as clinically meaningful reduction in DYS or NMPP plus stable or reduced analgesic use
EM-II, 2017[24,26] Phase III Parallel-arm RCT	6-month treatment period + 6 months of treatment in extension study; 12 months post-treatment follow-up	Placebo Elagolix 150 QD Elagolix 200 BID	N=817 Median age: 33 Age range: 18-49 Caucasian: 89% BMI (kg/m^2): 27	Clinical Responders (%) defined as clinically meaningful reduction in DYS or NMPP plus stable or reduced analgesic use
Tulip PETAL[22] Phase II Parallel-arm RCT with crossover	3-month treatment period until placebo and leuprorelin crossover; 3 months continued treatment	Placebo Elagolix 150 QD Elagolix 250 QD Leuprorelin acetate 3.75	N=174 Mean age: 31 (SD 1) Caucasian: 100% BMI (kg/m^2): 23	No primary outcomes-multiple pain measures (NRS/B&B)
PETAL[23] Phase II Parallel-arm RCT	6-month treatment period; 6-month post-treatment follow-up	DMPA-SC Elagolix 150 QD Elagolix 75 BID	N=252 Mean age: 32 (SD 0.6) Caucasian: 81% BMI (kg/m^2): 26	Change in Bone Mineral Density; multiple pain measures evaluated as secondary endpoints
Lilac PETAL[25] Phase II Parallel-arm RCT	3-month treatment period until placebo crossover; 3 months continued treatment; f/u 6 weeks post-treatment	Placebo Elagolix 150 QD Elagolix 250 QD	N=155 Mean age: 31 (SE 1) Caucasian: 81% BMI (kg/m^2): 27	Change in monthly mean pelvic pain NRS

F/U=follow-up; QD=daily; BID= twice a day; BMI=body mass index; DYS=dysmenorrhea; NMPP=nonmenstrual pelvic pain; NRS=numeric rating scale (0-10); B&B= Biberoglu and Behrman (0-3); VAS=visual analog scale (1-100)

Characteristics of the populations who participated in the Phase II and III trials of elagolix were generally similar, although patients in the Tulip PETAL trial had a lower mean BMI than women in other studies. All studies required participants to have symptomatic endometriosis with a

laparoscopically-confirmed diagnosis. The date of the laparoscopic surgery at which the diagnosis was made varied between 60 weeks and 10 years prior to enrollment in these studies. These patients may not be representative of the broader patient population with endometriosis in the US, who may have symptoms of variable duration and severity and be at various stages of diagnosis (some women may be treated with empiric therapies over several years before receiving a definitive diagnosis at the time of laparoscopy).

There were several other important differences across the trials of elagolix that prevented us from performing a quantitative synthesis of results. These differences are summarized in Tables 3.1 and 3.2. First, dosing of elagolix differed among the Phase II trials and between the Phase II and Phase III trials; only the 150 mg per day dose was constant among all the trials. Phase II studies included the 150 mg daily dose along with a split dose (75 mg twice daily) or a higher 250 mg daily dose. The two Phase III studies included the 150 mg daily dose but also added a new formulation, 200 mg twice a day, which had not been evaluated in prior trials.[23-25,22]

Second, efficacy outcomes differed across trials (Table 3.2). Although all studies included a version of the four-point Biberoglu and Behrman (B&B) pain scale to capture dysmenorrhea (DYS) and nonmenstrual pelvic pain (NMPP), the application of these scales and time of measurement varied.[27] Following the PETAL trial, in which pain was measured using monthly recall with the Composite Pelvic Signs and Symptoms Scale (CPSSS), FDA recommended using daily pain scores for dysmenorrhea and nonmenstrual pelvic pain.[34] Investigators modified the B&B pain scale for daily assessment in the Phase II Lilac PETAL trial. However, as reported in the results section below, no difference in nonmenstrual pelvic pain was observed between elagolix and placebo in this study. Consequently, manufacturers and FDA modified the wording of the B&B daily assessment questionnaire for implementation in subsequent Phase II and III trials.[34] The specific nature of these changes remains unclear.

Table 3.2. Pain Measures from Key Trials

	Pain Scales Used (Response Range)	Collection Frequency	Time Reported
EM-I and EM-II[24]			
	NRS (0-10)	Daily e-Diary	3 months
	DYS B&B (0-3)	Daily e-Diary	3 and 6 months
	NMPP B&B (0-3)	Daily e-Diary	3 and 6 months
	Dyspareunia B&B (0-3)	Daily e-Diary	3 months
Tulip PETAL[22]			
	NRS (0-10)	Daily	3 months*
	DYS B&B (0-3)	Daily	3 months*
	NMPP B&B (0-3)	Daily	3 months*
	Dyspareunia CPSSS B&B (0-3)	Monthly	3 months*
PETAL[23]			
	VAS (0-100)	Daily e-Diary	6 months
	DYS CPSSS B&B (0-3)	Monthly	6 months
	NMPP CPSSS B&B (0-3)	Monthly	6 months
Lilac PETAL[25]			
	NRS (0-10)	Daily e-Diary	3 months±
	DYS B&B (0-3)	Daily e-Diary	3 months±
	NMPP B&B (0-3)	Daily e-Diary	3 months±
	Dyspareunia CPSSS B&B (0-3)	Monthly	3 months±

*After 3 months, patients randomized to placebo or leuprorelin acetate were re-randomized to elagolix for 3 months; those taking elagolix continued treatment. ±After 3 months, patients randomized to placebo were re-randomized to elagolix for 3 months; those taking elagolix continued treatment. NRS=numeric rating scale; DYS=dysmenorrhea; B&B=Biberoglu

In addition to varying outcomes assessed, studies differed with respect to the definition of "clinical response." Only one of the Phase II trials defined clinical response. In the Phase II PETAL trial, patients who reported a reduction in pain (NMPP and DYS using the CPSSS) of one point or greater between baseline and week 24 were categorized as responders. In both Phase III trials, response was defined as a clinically meaningful reduction in the pain score as well as stable or reduced use of analgesics.[24]

To derive the minimal clinically important difference (MCID) for reduction in DYS and NMPP, the manufacturer used the Patient Global Impression of Change (PGIC) response at three months from each respective phase III study. The PGIC is a patient-reported outcome (PRO) that measures a patient's overall assessment of treatment efficacy.[50] It is assessed on a seven-point scale from "very much improved" to "very much worse."

To calculate the MCID, a receiver operating characteristic was created from those women who answered "very much improved" and "much improved" with the last recorded response being carried forward for all women who dropped out for any reason.[24] The difference in average score from the daily diaries between baseline and three months in all women who took one dose of study drug that correlated with the "very much improved" and "much improved" responses were calculated for dysmenorrhea and NMPP in each study. The MCID for EM-I was calculated to be a reduction of 0.81 points for DYS and 0.36 points for NMPP.[24] The MCID in EM-II was calculated to be a reduction of 0.85 points for DYS and 0.43 points for NMPP.[24] However, there is no reported standard for MCID on the B&B scale. Experts suggest B&B not be used as a primary endpoint in clinical trials.[29,30]

Other Studies of Elagolix Comparators

In addition to the elagolix trials reviewed, we identified three placebo-controlled trials of comparators from the NICE and Becker systematic reviews. These trials were published at least a decade prior to the Phase III trials of elagolix and included some differences in patient populations (see Appendix Table E1). Dlugi et al. was a six-month randomized placebo-controlled trial of leuprorelin acetate (3.75 mg IM monthly) versus placebo in 63 women in the U.S.[32] Similar to the elagolix trials, women had a surgical diagnosis of endometriosis and were at least 18 years of age. Endometriosis-related pain (NMPP, dyspareunia or pelvic tenderness) was required to be moderate-to-severe using the B&B scale.[32] Like the elagolix trials, moderate-to-severe dysmenorrhea alone was not enough to qualify.[32] Women were required to not have any endometriosis treatment in the prior three months and to be GnRH agonist naïve, but there was no run-in procedure identified.[32]

Ling et al. was a randomized placebo-controlled trial of leuprorelin acetate (3.75 mg IM monthly) in 100 women in the United States.[33] Women were between 18 to 45 years of age with moderate-to-severe chronic pelvic pain for six months (pain related to menstruation was not sufficient for study entry).[33] Unlike Dlugi or the trials of elagolix, women were not required to have a surgical diagnosis of endometriosis to enroll.[33] After the primary endpoint data was collected, laparoscopic confirmation was performed. Women were not allowed to have used contraceptives for three months or GnRH agonists for six months prior to enrolling.[33] There was also an imbalance in age between the arms (p=0.036).[33] The run-in protocol required multiple laboratory tests and provided a 10-day course of ibuprofen or naproxen with doxycycline for those without such treatment in the prior three months.[33]

One placebo-controlled trial of a hormonal oral contraceptive pill (OCP) with ethinylestradiol (0.035 mg) plus norethisterone (1 mg) was identified.[58] The study enrolled 100 women in Japan with symptomatic endometriosis or ovarian endometrioma diagnosed through laparoscopy or ultrasound, respectively.[58] Included women rated their dysmenorrhea to be moderate or severe

using a modified B&B scale that described pain in terms of productivity, impact on daily life and analgesic usage.[58] Of note, trials of elagolix excluded patients with endometriomas.[24] Other than requiring no medical or surgical treatment for eight weeks prior to enrollment, there was no run-in protocol described.[58] Current guideline recommendations view OCPs as a first-line treatment for women with endometriosis, therefore the Harada trial may have enrolled women that has less severe or impactful disease than women enrolled in the elagolix trials.

Quality of Individual Studies of Elagolix

Using criteria from the US Preventive Services Task Force (USPSTF [see Appendix E]), we judged the two Phase III randomized controlled trials (EM-I and EM-II) to be of good quality.[24,56] These studies were well designed (placebo-controlled, double blind), had balanced baseline characteristics between arms, and included a representative population. We deemed the three Phase II studies to be fair quality, due to some imbalance in baseline characteristics, incomplete reporting of outcomes, and modified intention-to-treat analysis. There was attrition in all studies that was comparable between arms. We did not rate the quality of the extension studies.

Clinical Benefits of Elagolix

Elagolix versus Placebo

In Phase III trials, elagolix provided statistically significant reductions in dysmenorrhea and nonmenstrual pelvic pain compared to placebo. Elagolix improved dysmenorrhea more than nonmenstrual pelvic pain and dyspareunia. High dose (200 mg twice daily) elagolix compared to placebo provided greater improvements in pain, quality of life, and decreased use of rescue opioids than 150 mg daily of elagolix. However, the comparative effects of elagolix in all trials have been measured over relatively short periods of time, ranging from eight weeks to six months and the criteria used to define a clinically meaningful reduction in symptoms had not been previously used.

Four of the five identified studies compared various doses of elagolix to placebo; head-to-head comparisons of elagolix versus leuprorelin acetate and elagolix versus subcutaneous depot medroxyprogesterone acetate (DMPA-SC) are reviewed in subsequent sections. Results of placebo comparisons from EM-I, EM-II, Tulip-PETAL, and Lilac-PETAL are described below.

<u>Clinical Response</u>

The primary outcome in the Phase III trials (EM-I and EM-II) was the proportion of patients with a clinical response at three months. Clinical response was defined as a clinically meaningful change in pain score as well as stable or reduced use of analgesics as described above (See "Key Studies"). This outcome was measured separately for dysmenorrhea and nonmenstrual pelvic pain. Table 3.3 below reports the results of this outcome for EM-I and EM-II at months three and six.

Table 3.3. Proportion of Women with a Clinical Response in EM-I and EM-II

		Dysmenorrhea (%)*		Nonmenstrual Pelvic Pain (%)*	
		3 Months	6 Months	3 Months	6 Months
EM-I[24]	Placebo	19.6	23.1	36.5	34.9
	Elagolix 150 QD	46.4	42.1	50.4	45.7
	Elagolix 200 BID	75.8	75.3	54.5	62.1
EM-II[24]	Placebo	22.7	25.4	36.5	40.6
	Elagolix 150 QD	43.4	46.2	49.8	51.6
	Elagolix 200 BID	72.4	76.9	57.8	62.2

*Elagolix 150 mg QD and 200 mg BID were statistically better ($p<0.05$) than placebo at 3 and 6 months

Given the similar findings between EM-I and EM-II, we highlight EM-I results since it restricted enrollment to patients from the U.S. and Canada. In EM-I, three quarters of women taking the high dose of elagolix (200 mg twice daily) reported a clinical response for dysmenorrhea at three and six months (see Table 3.3). This was an absolute difference from placebo of 56% at three months (97.5% CI, 49 to 64) and 52% (97.5% CI, 44 to 60) at six months.[24] Higher response rates were also seen for the 150 mg daily dose treatment arm, but the magnitude of the response was lower (42-46%). In EM-I, the 150 mg daily dose of elagolix provided a 27% difference from placebo in clinical response on dysmenorrhea (97.5% CI, 18 to 35) at three months.[24] This was reduced to 19% (97.5% CI, 2 to 20) at six months.[24] Our NNT analysis showed a need to treat approximately two to three patients with the 200 mg dose to achieve a clinical response in dysmenorrhea, while the figures range from four to six for the 150 mg dose (see Table 3.4).

Table 3.4. Number Needed to Treat* to Receive a Clinical Response in EM-I and EM-II

		Dysmenorrhea		Nonmenstrual Pelvic Pain	
		3 Months	6 Months	3 Months	6 Months
EM-I[24]	Placebo	-	-	-	-
	Elagolix 150 QD	4 (3 to 6)	6 (4 to 10)	8 (5 to 20)	10 (5 to 50)
	Elagolix 200 BID	2 (2 to 3)	2 (2 to 3)	6 (4 to 12)	4 (3 to 6)
EM-II[24]	Placebo	-	-	-	-
	Elagolix 150 QD	5 (4 to 9)	5 (4 to 9)	8 (5 to 25)	10 (5 to 100)
	Elagolix 200 BID	3 (2 to 5)	2 (2 to 3)	5 (4 to 9)	5 (4 to 9)

*Rounded to nearest full person (97.5% CI); derived by ICER

As shown in Table 3.3, there was a greater placebo response for nonmenstrual pelvic pain, and generally fewer women reporting a clinical response in the elagolix 200 mg group. In EM-I, 54% of women taking the 200 mg twice daily dose of elagolix reported a clinical response for nonmenstrual pelvic pain at three months and 62% at six months (see Table 3.3). This was a difference from placebo of 18% at three months (97.5% CI, 9 to 27) and 27% (97.5% CI, 18 to 36) at six months.[24] In EM-I, 150 mg daily dose elagolix provided a 14% difference from placebo in clinical response on nonmenstrual pelvic pain (97.5% CI, 5 to 23) at three months and 11% (97.5% CI, 2 to 20) at six

months.[24] Our NNT analysis showed somewhat higher values with nonmenstrual pelvic pain (4-6 and 8-10 for the 200 mg and 150 mg doses, respectively), but remained below generally-accepted ranges for NNT results (see Table 3.4).[59]

In a post hoc analysis of combined data from EM-I and EM-II, 56.4% of patients treated with the 200 mg twice daily dose of elagolix achieved a simultaneous response to dysmenorrhea and nonmenstrual pelvic pain at month 6 versus 17.2% of patients treated with placebo; results for the 150 mg daily dose have not been reported.[28]

Data from the two extension studies of EM-I and EM-II indicate that clinical response rates for dysmenorrhea and nonmenstrual pelvic pain were maintained in women who continued treatment with elagolix. At 12 months, dysmenorrhea response was 51-52% in the 150 mg daily dose cohort and 76-78% in the 200 mg twice daily dose cohort.[26] Nonmenstrual pelvic pain response was 66-68% in the 150 mg daily dose and 67-69% in the 200 mg twice daily dose group.[26] It is unclear why no dose response effect was seen for nonmenstrual pelvic pain response.

Other Pain Outcomes

Pain outcomes were reported using the numeric rating scale (NRS) for overall endometriosis-associated pain and the B&B scale for dysmenorrhea, nonmenstrual pelvic pain and dyspareunia for the two Phase III trials and two Phase II trials. Pain scores from the four placebo-controlled studies of elagolix are reported in Table 3.5 below.

At three months, overall endometriosis-associated pain using the NRS was statistically improved with both doses of elagolix in EM-I and EM-II; differences between elagolix and placebo did not reach statistical significance in phase II trials.[22,25] All doses of elagolix provided a statistically significant reduction in dysmenorrhea versus placebo at three months in Phase II and Phase III studies; differences were maintained through six months of therapy in Phase III trials. Nonmenstrual pelvic pain was also significantly improved at months three and six with both doses of elagolix in the Phase III trials, however differences were not statistically significant in the Tulip PETAL and Lilac PETAL Phase II studies.[22,24,25] Although changes from baseline were generally small, women in the Phase III and Phase II studies reported a decrease in dyspareunia pain irrespective of randomization arm. Decreases from baseline in dysmenorrhea, nonmenstrual pelvic pain, and dyspareunia scores were sustained over 12 months of treatment in the extension studies.[26]

Table 3.5. Mean Pain Scores in Placebo-Controlled Trials of Elagolix

		NRS		Dysmenorrhea			Nonmenstrual Pelvic Pain			Dyspareunia	
		Baseline	Week 12	Baseline	Week 12	Week 24	Baseline	Week 12	Week 24	Baseline	Week 12
EM-I[24]	Placebo	5.6	4.5	2.2	1.9	1.8	1.6	1.3	1.3	1.5	1.2
	Elagolix 150 QD	5.7	4.0*	2.2	1.2*	1.3*	1.6	1.2*	1.1*	1.5	1.1
	Elagolix 200 BID	5.5	3.1*	2.2	0.4*	0.5*	1.6	0.9*	0.9*	1.6	1.1*
EM-II[24]	Placebo	5.6	4.3	2.2	1.8	1.7	1.6	1.2	1.1	1.5	1.2
	Elagolix 150 QD	5.7	3.8*	2.2	1.2*	1.1*	1.7	1.1*	1.1*	1.5	1.1
	Elagolix 200 BID	5.3	2.8*	2.1	0.4*	0.5*	1.6	0.9*	0.8*	1.4	0.8*
Tulip PETAL[22Δ]	Placebo	3.3	2.1	1.4	0.9	NR	1.0	0.7	NR	NR	NR
	Elagolix 150 QD	3.7	2.2	1.3	0.5	0.5	1.1	0.7	0.6	NR	NR
	Elagolix 250 QD	3.3	1.8	1.1	0.4	0.3	0.9	0.6	0.5	NR	NR
Lilac PETAL[25]	Placebo	3.2	2.0	1.2	1.0	NR	1.0	0.6	NR	2.0	1.4
	Elagolix 150 QD	3.4	2.1	1.4	0.6*	0.6	0.9	0.6	0.6	2.0	0.9*
	Elagolix 250 QD	3.0	1.8	1.3	0.5*	0.5	0.8	0.6	0.5	1.9	1.2

Data were digitized from published charts and should be interpreted with caution. Δ Tulip PETAL also included leuprorelin acetate as an active comparator arm. These results are summarized in the subsequent section entitled "Elagolix versus GnRH Agonists"; *p<0.05 for LS mean change versus placebo; QD=daily; NRS=Numeric Rating Scale; NR=not reported

Patient Global Impression of Change (PGIC)

Patient global impression of change (PGIC) was reported in the Phase III trials, but not the Phase II trials. In EM-I and EM-II, approximately 75% of women who received the 200 mg twice daily dose of elagolix and 55-57% of women who received the 150 mg daily dose reported their endometriosis-related pain was "much or very much improved" from baseline compared to 31-35% of women who received placebo (both findings significant vs. all other categories, p<0.001).[24] After an additional six months of treatment in the extension studies (12 months total), 69-75% of patients who received the 150 mg daily dose and 84-91% of patients who received the 200 mg twice daily dose of elagolix reported their endometriosis pain to be "much or very much improved."[26]

Health Related Quality of Life

In EM-I and EM-II, the 200 mg twice daily dose of elagolix provided a statistically significant improvement in all six dimensions of the EHP-30 at three and six months compared to placebo.[24] The 150 mg daily dose of elagolix provided quality of life improvement versus placebo at both timepoints on three of six dimensions in EM-I (pain, control and powerlessness, and social support) and four of six dimensions in EM-II (pain, control and powerlessness, emotional well-being and social support).[24] After six additional months of treatment with elagolix in the extension studies

(12 months total), improvements were observed across all domains of the EHP-30 in both dose groups, although statistical comparisons between treatment groups were not performed.[26]

Phase II studies also found that the 150 mg daily dose of elagolix provided improved quality of life on the EHP-5 with the strongest results in the pain dimension; however, there was no statistically significant difference when compared to placebo.[22,25]

Analgesic Use

Use of analgesic pain medication was reported as part of the primary clinical response outcome in EM-I and EM-II. Change in mean monthly pill counts of NSAIDs and opioids were also reported separately to reflect use of rescue pain analgesics at three and six months compared to baseline. All arms, including placebo, reported reduced analgesic use.[24] At three months, women taking the 200 mg twice daily dose of elagolix reported significantly less opioid use compared to placebo (-0.08 to -0.12, SE 0.03; p<0.01) whereas the 150 mg daily dose did not (see Table 3.6).[24] In the extension studies, the least squares mean change in opioid pill count from baseline to 12 months was -0.13 to -0.20 in the 150 daily dose group and -0.25 to -0.27 in the 200 twice daily dose group.[26] Statistical comparisons between treatment groups were not performed in the extension studies.

Phase II studies showed that there was no difference in rescue analgesic use between the 150 mg daily dose of elagolix and placebo.[22,23,25]

Table 3.6. Number and Percent of Women Using Rescue Opioids at Baseline and Change from Baseline to Three-Months in the Phase III Trials of Elagolix

		Opioid Use at Baseline, n (%)	Change in Use from Baseline to 3- Months±	Difference from Placebo±
EM-I[24]	Placebo	71 (19.0)	-0.10±0.02	-
	Elagolix 150 QD	45 (18.1)	-0.07±0.03	0.03±0.04
	Elagolix 200 BID	53 (21.4)	-0.22±0.03	-0.12±0.04*
EM-II[24]	Placebo	56 (15.6)	-0.12±0.02	-
	Elagolix 150 QD	33 (14.6)	-0.12±0.02	0.00±0.03
	Elagolix 200 BID	28 (12.2)	-0.21±0.02	-0.08±0.03*

*p<0.01; QD=daily; BID=twice daily, ± least square-means and standard errors

Elagolix versus GnRH Agonists

The results of a single Phase II trial indicate that the GnRH agonist leuprorelin acetate appears to have better pain scores on the numeric rating scale, scales for dysmenorrhea and nonmenstrual pelvic pain, and the pain dimension of the EHP-5 compared to elagolix at 150 mg and 250 mg daily and placebo after 12 weeks of therapy. These findings are limited as they represent results from a single study that enrolled patients outside of the U.S., did not compare leuprorelin acetate to high dose elagolix (i.e., 200 mg twice daily), and did not universally report statistical testing between elagolix and leuprorelin acetate for all outcomes.

As previously described, elagolix has been directly compared to the GnRH agonist leuprorelin acetate in one study, the Phase II Tulip PETAL trial. This study was conducted in Eastern Europe using criteria similar to the other elagolix trials (see Table 3.1). Though all elagolix trials required patients to have an established diagnosis of endometriosis after laparoscopic surgery, Tulip PETAL required the diagnosis within 60 weeks, compared with seven to ten years in the other trials. Patient characteristics were similar compared to other elagolix trials with the exception that the population had a lower baseline BMI.[22]

We also searched two recent systematic reviews for placebo-controlled trials of FDA-approved GnRH agonists for inclusion in our review.[21,55] We identified two studies that were published in the 1990s.[32,33] Due to differences in when these studies were performed, as well as eligibility criteria and patient characteristics, we did not perform an indirect comparison with elagolix. These studies and their results are summarized in the appendix (see Appendix Section E).

Clinical Response

Clinical response was not reported in the Phase II Tulip PETAL trial of elagolix versus leuprorelin acetate.

Other Pain Outcomes

At week 12, pain scores were lowest for leuprorelin acetate on the Numeric Rating Scale (NRS), and measurements of Dysmenorrhea, and Nonmenstrual pelvic pain (NMPP). Statistical differences were only reported for NMPP ($p<0.05$ for leuprorelin acetate vs. both doses of elagolix).[22] As a reminder, the NRS is a scale of 0-10 (no pain to worst pain) and the B&B scale for dysmenorrhea and NMPP are 0-3 (no pain to severe pain). Table 3.7 summarizes the 12-week pain scores for each of the arms in the study.

Table 3.7. Mean 12-Week Pain Scores from the Tulip PETAL Trial[22]

	NRS		Dysmenorrhea		Nonmenstrual Pelvic Pain	
	Baseline	Week 12	Baseline	Week 12	Baseline	Week 12
Placebo	3.3	2.1	1.4	0.9	1.0	0.7
Elagolix 150 QD	3.7	2.2	1.3	0.5	1.1	0.7
Elagolix 250 QD	3.3	1.8	1.1	0.4	0.9	0.6
Leuprorelin Acetate 3.75	3.1	1.4	1.3	0.1	0.9	0.4

Data were digitized from published charts and should be interpreted with caution. QD=daily; NRS=Numeric Rating Scale

At week 12, patients treated with leuprorelin acetate had significantly greater mean improvement from baseline in dyspareunia compared with placebo (-1.04 vs. -0.60, p=0.0059); scores for elagolix were not reported.

Patient Global Impression of Change (PGIC)

PGIC was not reported in the Tulip PETAL Study.[22]

Health Related Quality of Life

Between baseline and week 12, all treatment groups reported improvements across the five dimensions of the EHP-5. Improvements were comparable for all dimensions except pain, for which patients who were treated with leuprorelin acetate reported greater improvements than those in each elagolix group (-31.8 ±3.9 with leuprorelin acetate vs. -19.0 ± 4.1, p=0.006 and -25.0 ± 4.7, p=0.0204 for elagolix 150 and 250 mg, respectively). Investigators noted that these results indicated a higher efficacy of leuprorelin acetate in the pain dimension of the EHP-5.

Analgesic Use

The mean percentage of days with analgesic use ranged from 10-15% at baseline among treatment groups. After 12 weeks of treatment, analgesic use decreased by 6.2%, 4.4%, 8.3%, and 10.5% in the placebo, elagolix 150 mg, elagolix 250 mg, and leuprorelin acetate groups, respectively.[22] There were no significant differences between elagolix or leuprorelin acetate compared with placebo; statistical testing between active treatment arms was not reported. Of note, the trial permitted the use of only mild analgesics (e.g., ibuprofen, naproxen) as rescue therapy and analgesic use was acknowledged to be relatively low at baseline.

Elagolix versus Hormonal Contraceptives

Subcutaneous depot medroxyprogesterone (DMPA-SC) was compared to elagolix 75 mg twice daily and 150 mg daily in one head-to-head Phase II trial. Elagolix provided similar response to DMPA-SC and was comparable in all pain and quality of life outcomes as well as use of opioid analgesics.

Elagolix was compared to subcutaneous depot medroxyprogesterone acetate (DMPA-SC) in one Phase II non-inferiority trial (the PETAL trial).[23] Results are described below.

We also searched two recent systematic reviews for placebo-controlled trials of FDA-approved hormonal therapies for inclusion in our review.[21,55] We identified one randomized, double-blind, multicenter trial of monophasic ethinylestradiol plus norethisterone (an OCP) versus placebo.[58] Due to differences in when this study was performed, its location, as well as eligibility criteria and patient characteristics, we did not perform an indirect comparison with elagolix. This study and its results are summarized in the appendix (see Appendix Section E).

Clinical Response

This Phase II trial involved an analysis of response using the dysmenorrhea and nonmenstrual pelvic pain components of the CPSSS to establish noninferiority of the two dosing regimens of elagolix versus DMPA-SC.[23] Patients who reported a reduction in pain of one point or greater between baseline and week 24 were categorized as responders. The difference in response rate for both dysmenorrhea and nonmenstrual pelvic pain was calculated for each elagolix dose versus DMPA-SC; statistical noninferiority was defined to have been met when the lower limit of the 95% confidence interval for the difference was no less than -20%.[23]

At week 24, the proportion of patients who reported an improvement in dysmenorrhea was 86.0% in the elagolix 150 mg daily group, 73.8% with elagolix 75 mg twice daily, and 86.3% with DMPA-SC. The dysmenorrhea response was not statistically different between the elagolix arms and DMPA-SC.[23]

Similar to dysmenorrhea, NMPP response did not statistically differ between the two elagolix dosing regimens and DMPA-SC (86.0%, 76.9%, and 76.5% for the elagolix 150 mg, elagolix 75 mg, and DMPA-SC groups, respectively; p=NS).[23]

Other Pain Outcomes

Carr and colleagues evaluated pelvic pain as a secondary endpoint in the PETAL trial (see Table 3.8). Pain was measured using the least square mean change from baseline for the total CPSSS. In all three groups, comparable yet clinically meaningful (defined as a mean reduction of ≥4 points from baseline) improvements were observed.

Similarly, patients reported an improvement in pelvic pain across all three intervention arms when measured by monthly mean VAS. The mean change from baseline was similar between the DMPA-SC and elagolix 150 daily group, with slightly greater improvements observed in the elagolix 75 twice daily group.[23]

The mean dysmenorrhea score from the CPSSS improved by week four across all study arms and was maintained through week 24 of treatment. Each group reported a mean reduction in dysmenorrhea of approximately 1.5 points.[23] After discontinuation of study therapy, mean dysmenorrhea scores worsened by almost a full point in all groups but did not return to baseline levels as of week 48.[23]

An improvement in NMPP of approximately one point was reached by week 8 in each treatment arm and was maintained through week 48 after withdrawal of study drug.[23]

Patient-reported improvement in dyspareunia was slower, reaching a meaningful improvement by week 12 for the elagolix 150 mg daily group and week 16 for the 75 mg twice daily group; dyspareunia improved with DMPA-SC as well, but mean scores did not cross the study-defined clinically meaningful improvement of 1 point at any timepoint during 48 weeks of follow-up.[23]

Table 3.8. Change from Baseline in Mean Pain Scores from the PETAL Trial[23]*

	CPSSS$^{\alpha}$	VAS$^{\beta}$		Dysmenorrhea		Nonmenstrual Pelvic Pain		Dyspareunia	
	Week 24	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24	Week 12	Week 24
DMPA-SC	-5.3	-15.7	-17.0	-1.5	-1.7	-0.9	-1.1	-0.6	-0.9
Elagolix 150 QD	-5.5	-17.7	-18.2	-1.4	-1.5	-1.0	-1.2	-1.0	-1.2
Elagolix 75 BID	-5.2	-23.6	-23.6	-1.7	-1.4	-1.1	-1.2	-0.9	-1.0

Data were digitized from published charts and should be interpreted with caution; *Baseline scores were not reported; α Week 12 scores were not reported; β VAS was scored on a scale of 0 (no pain) to 100 (worst pain ever felt). Patients indicated the worst level of pain felt over a 24-hour period; CPSSS=Composite Pelvic Signs and Symptoms Score; VAS=Visual Analog Scale; QD=daily; BID=twice daily

Patient Global Impression of Change (PGIC)

PGIC was not reported in the PETAL Trial.[23]

Health Related Quality of Life

Carr et al. assessed quality of life using the EHP-5 questionnaire. Comparable improvements were reported across all five core dimensions in all three treatment groups at the end of 24 weeks; statistical testing of between-group differences was not reported.

Analgesic Use

A greater proportion of patients in the DMPA-SC group reported opioid use at baseline compared to the two elagolix arms (28.9% vs. 21.4% and 19.0% in the 150 mg and 75 mg groups, respectively).[23] At week 24, opiate use increased slightly in each arm by similar amounts (33.7%, 23.8% and 25.0% in the DMPA-SC, elagolix 150 mg, and elagolix 75 mg arms, respectively).[23]

Elagolix versus Aromatase Inhibitors

We found no trials that directly compared the efficacy of elagolix and aromatase inhibitors.

There are currently three FDA-approved aromatase inhibitors: anastrozole, letrozole and exemestane, all of which are indicated as adjunctive therapies for breast cancer in postmenopausal women.[60] Our literature review did not identify any studies comparing aromatase inhibitors to elagolix or placebo in patients with endometriosis. Nevertheless, for context, we summarize the findings of a systematic review of aromatase inhibitors for endometriosis pain in Appendix E.

Summary of NICE Systematic Review and Network Meta-Analysis

In September 2017, the National Institute for Health and Care Excellence (NICE) in the UK published a clinical guideline on the diagnosis and management of endometriosis (see Section 2.2 of this report for a summary of the Guideline Committee's recommendations).[21] The guideline included a systematic literature search evaluating the clinical efficacy and cost effectiveness of hormonal medical treatments in treating symptoms of pain in women with endometriosis. Treatment classes included danazol/gestrinone, estrogens, progestogens, GnRH agonists, GnRH antagonists, and aromatase inhibitors.

Network meta-analysis (NMA) was performed to synthesize evidence on pain relief, health-related quality of life, and adverse events. Due to the sparseness of the networks, the NMA grouped treatments by class and assumed a common class effect. In most cases, there was insufficient evidence to assess within-class differences. The population of focus was women with laparoscopic confirmation of endometriosis. Some trials included women with endometriomas while some did not. This is notable because women with endometriomas may have a different response to treatments for pain relief. The included studies also varied in relation to the duration of therapy and/or study follow-up, as well as dosing. Sensitivity analyses were performed to account for heterogeneity.

To evaluate pain, investigators incorporated various pain scales including the dysmenorrhea and nonmenstrual pelvic pain subscales from Biberoglu and Behrman using a Bayesian multivariate fixed effects model. They included fifteen trials of ten hormonal treatment classes –a total sample size of 1,680 women –for their network with the outcome of pain relief. The NMA found that all treatments led to a clinically significant reduction in pain (defined as a difference of 10 points on a

0-100 VAS scale) when compared to placebo. The magnitude of this effect was similar for all treatments, with no material differences observed between them. However, NICE indicated that there was inconsistency between the indirect comparisons and direct comparisons, especially for the intrauterine progestogens and intramuscular GnRH agonists. A univariate model showed these therapies to be more effective than the multivariate model. Furthermore, the model was subject to the limitations listed above (e.g., sparse network and inclusion of women with endometriomas).

Investigators included five trials of four treatment classes in the network, with a total sample size of 572 women, in their analysis of dyspareunia. Dyspareunia was assessed using the scale developed by Biberoglu and Behrman, a patient-reported scale of 0-3. Similar to the VAS analysis results, all treatments were associated with a small but significant improvement over placebo in dyspareunia.

The NMA results led the guideline Committee to support the use of hormonal treatments for pain management without recommending any specific therapy. The Committee maintained that first-line therapy with an oral combined contraceptive or progestogens would have good efficacy and more tolerable side effects. When first-line hormonal treatment was contraindicated or not tolerated, they recommended that women be referred to a gynecologist for further treatment which could include other hormonal therapies or surgery. Other therapies such as GnRH agonists were considered effective but had higher risk of discontinuation due to adverse events, caused more serious adverse events such as bone density changes, and were indicated for shorter durations of therapy.

Harms of Elagolix

The most common side effects of elagolix are hot flash, headache, and nausea. Bone mineral density loss is significantly greater than placebo at the 150 mg daily and the 200 mg twice daily dose at six months. After 12 months of continuous treatment without add-back hormonal therapy, 2-8% of women taking the 150 mg once daily dose and 21% taking the 200 mg twice daily dose of elagolix had lost more than 8% of their BMD.[16] Studies did not report how BMD loss translates into future risk of osteoporosis or fracture. Alterations in lipid profiles (elevated total cholesterol, LDL cholesterol, and triglycerides) may make women at higher risk for cardiovascular events. There were no long-term data on cardiovascular events reported in the trials. The FDA prescribing information also highlighted warnings about elevated liver function tests, suicidal ideation, and reduced ability to recognize pregnancy.

<u>Death and Suicidal Ideation</u>

No deaths were reported in Phase II trials and one death was reported in the Phase III trials. A patient who received 150 mg daily of elagolix for approximately 30 days in the EM-II trial overdosed with multiple non-trial related medications; the death was deemed a suicide.[24] The patient had no relevant past medical history.[16] Among 2,090 women who were exposed to elagolix during Phase II and III studies, there were four reports of suicidal ideation; three of these patients had a history of

depression.[16] FDA prescribing information for elagolix includes a warning for suicidal ideation and mood disorders.

A second death was mentioned only in the protocol appendix of EM-I and EM-II.[24] The patient was taking elagolix and the death was attributed to alcoholic liver disease in a woman with severe hepatic impairment (see information below on abnormal liver function tests).[24]

Discontinuation due to Adverse Events

Rates of discontinuation due to adverse events (AEs) are reported in Table 3.9. Women who received placebo and elagolix 150 mg daily in the EM-I and EM-II trials reported similar rates of discontinuation due to AEs (5.9-6.1% and 4.4-6.4%, respectively).[24] Approximately 9-10% of women in the 200 mg arm discontinued study treatment due to adverse effects. During the six-month extension studies, rates of discontinuation due to adverse events were similar to those of the Phase III trials: 4.0-5.6% of patients treated with the 150 daily dose of elagolix and 8.7-9.3% of patients treated with the 200 mg twice daily dose discontinued study therapy.[26] The most common reason for discontinuation was decreased bone mineral density (>8% decrease required discontinuation).

The placebo-controlled trial of leuprorelin acetate from Dlugi and colleagues reported that 1 patient (4%) discontinued therapy due to AEs.[32] Trials in which patients were treated with leuprorelin acetate for a shorter duration, namely the Phase II Tulip-PETAL study of elagolix versus leuprorelin acetate and the placebo-controlled trial from Ling et al. (1999), also reported low rates of discontinuation due to AEs (0-2%).[22,33]

Although the incidence of AEs was similar across intervention arms in the PETAL trial of elagolix versus DMPA-SC, more patients in the DMPA-SC group discontinued therapy due to an adverse event (17% vs. 5% and 8% in the elagolix 150 mg and 75 mg groups, respectively).[23]

Adverse Events (AEs)

Specific adverse event frequencies are reported in Table 3.9. Serious adverse events were uncommon in the elagolix trials across all intervention arms. The most frequently reported AEs in EM-I and EM-II included headache, hot flash, and nausea.[24] Patients treated with the 200 mg dose of elagolix reported higher rates of hot flash than patients in the 150 mg and placebo groups. Investigators noted that the majority of women reporting hot flashes rated the maximum severity as mild or moderate.

Table 3.9. Adverse Events Occurring During Six Months of Treatment (%)[Δ]

	Placebo[24]	Elagolix 150 mg[24]	Elagolix 200 mg[24]	Leuprorelin Acetate[31,32]*	DMPA-SC[23]
Any AE leading to DC	6	4 – 6	9 - 10	4[α]	17
Any serious AE	3	1 – 5	2 - 3	NR	4
Acne	4 - 5	3 – 5	4	10	8
Amenorrhea	0.3	3 – 5	6 - 9	98	NR
Anxiety	3 - 4	2 – 4	4 - 7	<5%	5
Arthralgia	2 - 3	3 – 4	3 - 7	NR	2
Back pain	4 - 7	4	4 - 6	NR	5
Depression	2 - 3	2 – 4	2 - 5	22	5
Fatigue	4 - 6	4 – 6	4 - 7	3	7
Headache	10 - 14	15 - 19	17 - 23	32	18
Hot flash	7 - 10	23 - 24	42 - 48	84	76§
Insomnia	2 - 3	6	7 - 11	<5%	5
Mood swings	2 - 3	4 – 6	3 - 4	NR	12
Nausea	11 - 14	10 - 12	16	13[β]	16
Night sweats	0.3 - 1	1 – 2	2 - 6	NR	NR

AE=adverse event, DC=discontinuation, NR=not reported Δ Ranges indicate differences between EM-I and EM-II; * AEs of leuprorelin acetate were collected from the FDA Prescribing Information except where otherwise indicated; α Dlugi et al. (1990); β Reported as nausea/vomiting; DMPA-SC=Subcutaneous depot medroxyprogesterone; §All arms of PETAL reported a high proportion of women reporting hot flash.

Table 3.9 includes rates of adverse events from the FDA Prescribing information for leuprorelin acetate and from the Phase II PETAL trial of DMPA-SC versus elagolix. Patients who participated in the PETAL trial reported similar incidence of AEs across arms.[23] Data for leuprorelin acetate in FDA publications report higher rates of amenorrhea, depression, headache, and hot flash than noted in the elagolix trials.[31]

Aromatase inhibitors are not FDA-approved for endometriosis treatment but carry similar side effects in comparison to other hormonal treatments.[61,62] Hot flashes, arthralgia, asthenia, arthritis, edema, headache, dizziness, sweating, bone pain, pharyngitis, depression, nausea/vomiting, rash, insomnia and musculoskeletal discomfort are reported.[61,62]

Bone Mineral Density

Both doses of elagolix significantly reduced bone mineral density at the lumbar spine, femoral neck and total hip compared to placebo in the Phase III trials, with the magnitude being dose dependent (see Table 3.10).[24] In EM-I, 1.1% of women in the elagolix 150 mg group and 3.3% in the 200 mg group had a z-score for bone mineral density at the lumbar spine that was -1.5 or less after 6 months of treatment (vs. 0.4% in the placebo group). In EM-II, 0%, 0.6%, and 4.9% in the placebo, elagolix 150 mg and elagolix 200 mg groups, respectively, passed this same threshold.

Table 3.10. Mean Percent Change in Bone Mineral Density[24]

Bone Mineral Density Change from Baseline to 6 Months						
	Lumbar Spine		Total Hip		Femoral Neck	
Elagolix 150 mg daily						
	EM-I	EM-II	EM-I	EM-II	EM-I	EM-II
Difference from Placebo (%)	-0.79	-1.28	-0.54	-1.05	-0.41	-0.66
95% Confidence Interval	-1.29, -0.30	-1.75, -0.80	-0.93, -0.15	-1.46, -0.64	-1.02,0.20	-1.23, -0.10
P-value	<0.01	<0.001	<0.01	<0.001	NS	<0.05
Elagolix 200 mg twice daily						
	EM-I	EM-II	EM-I	EM-II	EM-I	EM-II
Difference from Placebo (%)	-3.08	-3.04	-1.74	-2.16	-1.91	-1.73
95% Confidence Interval	-3.58, -2.59	-3.51, -2.58	-2.13, -1.35	-2.57, -1.76	-2.53, -1.29	-2.28, -1.17
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

NS=nonsignificant

In addition to numeric reporting of mean percent change, women were classified into categories based on percent of bone loss: less than or equal to 3%, 3-5%, 5-8% and greater than or equal to 8%. In EM-I, 4% of patients treated with the 150 mg daily dose of elagolix and 20% of patients treated with the 200 mg twice daily dose had a decrease in BMD at the lumbar spine greater than 5%.[24]

Extension studies of patients receiving elagolix in the phase III trials show that 2-3% of the 150 mg daily dose group and 26-30% of the 200 mg twice daily dose group had a decrease of 5-8% in lumbar spine BMD after 12 months of continuous treatment. The percentage of women with more than an 8% decrease in BMD in the lumbar spine, total hip, or femoral neck was 2-8% with the 150 mg once daily dose and 21% with the 200 mg twice daily dose.[16] These rates represent ongoing loss since women were excluded from participating in the extension studies if they already had a BMD loss of 8% or more after the first six months of treatment. Of the 741 patients who completed 6 months of treatment in the Phase III studies, 1% of patients treated with 150 mg daily and 7% of patients treated with 200 mg twice daily did not enroll in the extension study as a result of these dual-energy X-ray absorptiometry (DXA) findings.

Phase II studies show similar significant reductions in bone mineral density for the 150 mg daily dose elagolix compared to placebo.[22,25] The Tulip PETAL study reported greater decreases in BMD in the leuprorelin acetate arm compared to 150 mg daily of elagolix. A mean percentage change in spinal BMD from baseline to three months was reported as -1.63 (95% CI -2.28 to -0.99) in the leuprorelin acetate arm, -1.05 in the 150 mg daily dose elagolix arm (95% CI -1.68 to -0.43) and 0.11 in the placebo arm (95% CI -0.50 to 0.71).[22] The mean percentage change in femur BMD from

baseline to three months was also highest in the leuprorelin acetate arm (-1.12, 95% CI -1.63 to -0.62) compared to the elagolix 150 mg daily (-0.34, 95% CI -0.84 to 0.16) and placebo arms (-0.90, 95% CI -0.51 to 0.33).[22] No statistical comparisons between arms were performed.[22]

At week 48 (24 weeks after completing therapy with elagolix), 55 patients across all intervention arms of the Tulip PETAL trial had repeat bone scans. Between weeks 24 and 48, BMD at the femur remained unchanged in these patients, while the change from baseline in spinal BMD reduced; none of the participants had abnormal z-scores.[22]

Recovery of bone density after stopping elagolix was evaluated in two extension studies that included up to one year of therapy and one year follow-up post-therapy.[26] These studies showed improvement, but levels did not return to baseline in many patients. In one of the extension studies (EM-IV), 50% of the women in the 150 mg group and only 34% in the 200 mg group who had a decrease in lumbar spine BMD after 12 months of continuous elagolix had at least a 50% improvement six months after discontinuation of therapy; similar improvements in total hip and femoral neck BMD were reported for only 32-36% of patients in both dosing groups as well.[26,63] The question of whether BMD loss is ultimately reversible is still under evaluation.

FDA prescribing information for elagolix includes warnings about dose- and duration-dependent decreases in bone mineral density that may not be completely reversible.[16] As a result, elagolix is only approved for six months of therapy at the 200 mg twice daily dose. At the 150 mg daily dose, elagolix is approved for up to 24 months. However, due to concerns that hepatic impairment may increase levels of elagolix and therefore increase risk of bone loss, women with moderate hepatic impairment should only take the lower dose of elagolix and limit treatment duration to six months.

The FDA label for leuprorelin acetate states that bone mineral density loss may not be reversible and recommends providing add-back hormones and calcium supplementation to protect from bone loss.[31] The FDA states that the duration of leuprorelin acetate treatment should be no longer than six months.[31] FDA labels for the aromatase inhibitors letrozole and anastrozole also include warnings about reductions in bone mineral density leading to the potential for fracture and osteoporosis.[61,62]

Lipid Profile Changes

Higher LDL cholesterol levels and lower HDL cholesterol levels are known risk factors for cardiovascular disease. In EM-I and EM-II, total cholesterol and LDL cholesterol increased significantly in both elagolix arms compared with placebo.[24] These increases were greatest with the 200 mg twice daily dose of elagolix (see Table 3.11). Triglycerides also increased significantly relative to placebo in the 200 mg twice daily elagolix group. However, HDL cholesterol levels were also significantly elevated between baseline and six months compared to placebo in the 200 mg twice daily dose elagolix arm.[24] In patients who received continuous treatment with elagolix for 12

months during the extension studies, the mean total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides were less than 2 mg/dL above baseline levels at one month post-treatment.[26]

Table 3.11. Percent Change from Baseline to Six Months in Serum Lipid Levels During Phase III Trials of Elagolix

	EM-I			EM-II		
	Placebo	Elagolix 150 mg Daily	Elagolix 200 mg Twice Daily	Placebo	Elagolix 150 mg Daily	Elagolix 200 mg Twice Daily
Total cholesterol	-0.71±12.08	5.10±13.05	13.46±13.86	-0.56±11.80	4.55±11.78	10.40±14.95
LDL cholesterol	-2.03±19.53	6.55±20.63	17.08±21.55	-0.70±19.53	5.73±19.00	13.04±23.35
HDL cholesterol	4.04±17.20	5.07±15.86	8.19±16.08	1.44±15.77	4.48±14.76	7.72±17.52
Triglycerides	6.73±44.29	10.00±45.80	25.28±51.26	3.82±40.53	7.74±40.52	18.08±48.61

Mean ± SD

Leuprorelin acetate can also increase cholesterol values. In a clinical trial summarized in the FDA prescribing information, 7% of women receiving leuprorelin acetate who entered the study with normal cholesterol at baseline ended with total cholesterol above normal range.[31] Triglycerides increased to above normal limits in 12% of the leuprorelin acetate arm of the same study.[31] In their review of leuprorelin acetate, the FDA stated that "the long-term significance of the observed treatment-related changes in serum lipids in women with endometriosis is unknown."[31]

FDA labels for the aromatase inhibitors letrozole and anastrozole included language about hypercholesterolemia, including warnings for women with pre-existing cardiac conditions. [61,62]

Teratogenic Effects

Though women were supposed to use two forms of birth control, there were 23 pregnancies documented in the Phase III trials. While not technically considered a harm, we summarize these results as an unintended consequence and review whether any children born as a result of these pregnancies showed evidence of any teratogenic effects associated with elagolix treatment.

Of the pregnancies identified, 15 were in the placebo arm and 8 were in the elagolix arms (six at a dose of 150 mg daily, two at a dose of 200 mg twice daily).[24] Pregnancies included five lost to follow-up, one stillbirth, one ectopic pregnancy, three terminations, four spontaneous abortions and nine live births.[24] There were three healthy births in women taking elagolix, with no anomalies reported.[24]

Ten additional pregnancies occurred during the extension studies, of which four resulted in normal live births, two were lost to follow-up, and three were terminated. The remaining pregnancy also resulted in a normal live birth, although the infant was later diagnosed with a craniosynostosis. There is no evidence the fetus was exposed to elagolix.[26]

At least four pregnancies were reported in earlier elagolix studies.[34] Of those, two resulted in healthy babies, while one cleft palate and one tracheal fistula were reported.[34] While neither outcome was deemed attributable to elagolix, the company acknowledges that the effect of elagolix on pregnancy is still uncertain.[24,34] Preclinical studies did not identify any teratogenic effects of elagolix.[34]

Liver Function

The FDA labels for the GnRH agonists report abnormal elevations in markers of liver function in a small number of patients.[31,64,65] There was no evidence of liver function abnormalities mentioned in the published elagolix studies. However, FDA prescribing information reports dose-dependent elevations in serum alanine aminotransferase (ALT) to at least 3-times the upper limit of the reference range were observed during the Phase III trials and extension studies of elagolix.[16] The FDA prescribing information includes a warning for hepatic transaminase elevations and specifies that elagolix is contraindicated for patients with severe hepatic impairment.[16]

Controversies and Uncertainties

Several important limitations in the available evidence about the comparative benefits and harms of elagolix are worth highlighting. Differences in the Phase II and Phase III studies of elagolix versus placebo and active comparators included variability in the total and frequency of elagolix dosing, duration of therapy, choice of endpoints, how endpoints were analyzed, and data presentation. These differences precluded the ability to perform quantitative indirect comparisons of elagolix regimens in our review.

As described in the Key Studies section, dosing of elagolix has changed over time. The two Phase III studies included a new formulation, 200 mg twice a day, which was not evaluated in prior trials.[22-25] This new formulation represents the highest daily dose to be tested of elagolix, and initial evidence from EM-I and EM-II suggest a dose-response relationship in terms of both efficacy and safety. Hypoestrogenic adverse effects such as loss of BMD were greater with elagolix 200 mg twice a day than that observed with lower doses of the drug. It is notable that a trial comparing 150 mg once daily versus 75 mg twice daily (150 mg total) of elagolix resulted in greater bone density loss with twice daily dosing. This may imply that the frequency of dosing as well as the total dose may be important in assessing drug safety.

Endometriosis is recognized as a chronic condition with no available treatment demonstrating cure or long-term control of symptoms. The short duration of therapy with elagolix versus placebo or other active comparators means it is difficult to extrapolate the benefits and risks of long-term use. Available comparative data assessed elagolix versus placebo at three or six months. The longest duration of use is 12 months from the blinded extension trials, yet low-dose elagolix (150 mg daily)

has been approved for up to 24 months of use in patients with normal liver function or mild hepatic impairment.[16,26,63,66,67]

In addition to differences in dosing administration and duration, a variety of pain outcomes were assessed across key studies of elagolix. The primary outcome in the Phase III trials, clinical response, was not used in Phase II trials or any other trial that we were able to identify. EM-I and EM-II assessed composite co-primary endpoints of clinical response at three months for dysmenorrhea and nonmenstrual pelvic pain. Response was defined as a clinically meaningful reduction in pain as well as stable or reduced use of analgesics.[24] A single pain outcome reflecting an overall weighting of dysmenorrhea and nonmenstrual pelvic pain was only reported in a post hoc analysis of combined data from EM-I and EM-II and has only been reported for the 200 mg twice daily dose of elagolix.[28] To further complicate matters, the minimal clinically important difference (MCID) for reduction in dysmenorrhea and nonmenstrual pelvic pain was derived separately for EM-I and EM-II using differences relative to patient reported global impression of change (PGIC). The use of the PGIC was required because there is no validated MCID for the B&B scale, which may account for why the B&B is not recommended as a primary endpoint in clinical trials.[29]

Consensus statements have recommended daily rating of dysmenorrhea and pelvic pain using an 11-point numeric rating scale (NRS).[30] However, the Phase III studies modified the four-point B&B scale for daily rating, and only examined NRS for overall pelvic pain at three months compared to baseline. While the Phase II studies also included the four-point B&B pain scale to assess dysmenorrhea and nonmenstrual pelvic pain, both the wording and timing (from monthly recall to daily diary entries) were modified during Phase II development under guidance from the FDA.[34]

In terms of data presentation, the Phase II studies did not consistently include sufficient baseline demographic data to assess comparability across studies. To report baseline dysmenorrhea and nonmenstrual pelvic pain means/medians between arms, we were often forced to estimate values by digitizing figures. Complete presentation of key baseline and follow-up data is critical in reporting data from clinical trials.

In addition to comparing elagolix to placebo, we also sought out data comparing elagolix to other medical therapies for endometriosis including GnRH agonists, contraceptive hormones, and aromatase inhibitors. Our review did not identify robust head-to-head data of elagolix versus the comparators of interest but did include two Phase II trials with an active comparator. One study included the GnRH agonist, leuprorelin acetate, while the other compared the progestin, depot medroxyprogesterone acetate. While both had methodological challenges, they offer the only head-to-head evidence available. These studies included relatively short durations of follow-up and/or crossover, high rates of attrition, omission of crucial baseline characteristics (e.g., baseline pain scores were not reported in the study from Carr et al., 2014), imbalances in baseline characteristics, and a lack of statistical testing between active study arms.[22,23]

To provide additional context, we searched for placebo-controlled trials of comparators from recent published systematic reviews. We found three placebo-controlled trials, two of leuprorelin acetate and one with an OCP. However differences in these studies relative to trials of elagolix meant we were unable to synthesize data through quantitative indirect comparison.[21,32,33,44,55,58]

In the absence of curative therapy, patients with endometriosis are often treated with multiple courses of medical therapy and surgery. Like other medical therapies, there are no studies of the comparative effectiveness of elagolix versus surgery. It is also not known whether medical therapies including elagolix may delay, limit or prevent the need for future surgery.

Finally, there is significant uncertainty around the harms of elagolix. Though the Phase III trials reported dose-related adverse side effects for elagolix, rates of discontinuation were low. Bone mineral density (BMD) loss is a well-recognized side effect. It has been proposed that the dose-dependent nature of ovarian hormone suppression with elagolix may permit dosing that improves symptoms while avoiding bone loss such as seen with leuprorelin acetate, however clinical data to support this claim remains uncertain.[35] In blinded extension studies examining elagolix use up to 12 months, most women had some level of bone mineral loss, with higher rates and degrees of bone loss in women in the 200 mg twice daily group. Studies evaluating post-treatment bone density so far show decreases in bone loss that do not return to pre-treatment levels.

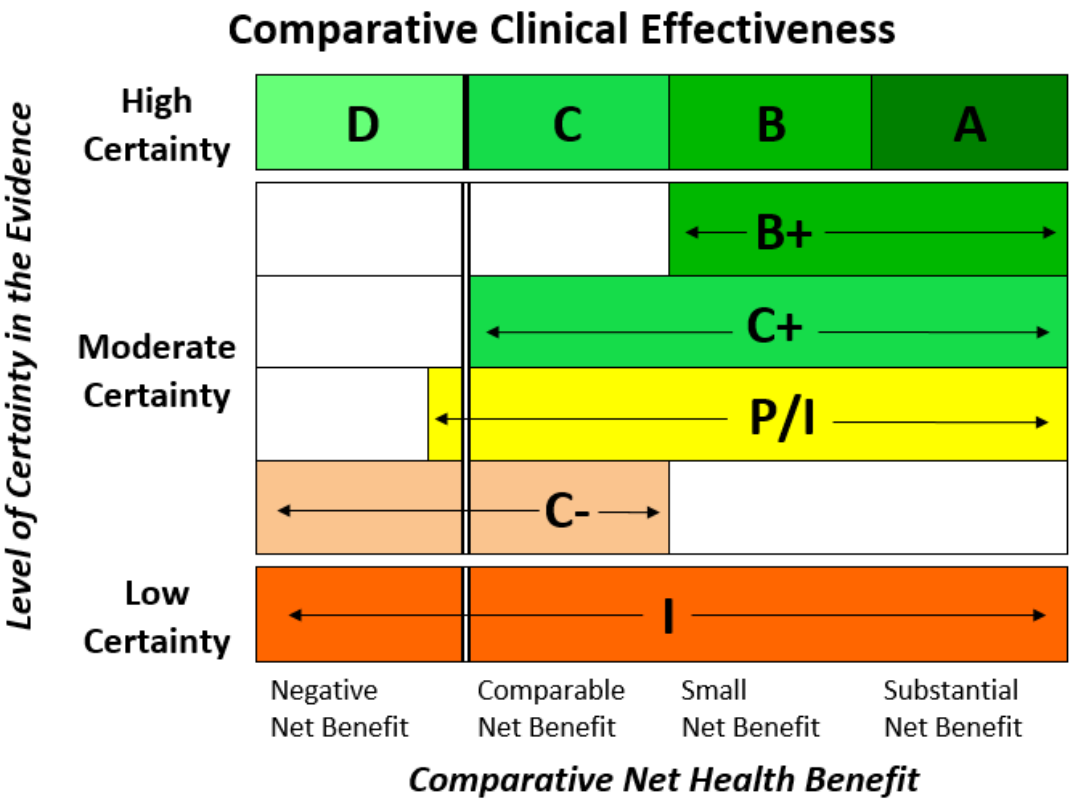
To prevent bone loss with prolonged use of GnRH agonists, add-back contraceptive hormones are recommended. Though no published studies have reported using add-back therapy for elagolix in patients with endometriosis, it may be expected that such therapy would be considered for long-term use of higher doses of elagolix. However, FDA prescribing information urges caution in using estrogen-containing hormonal contraception because it may decrease the efficacy of elagolix. As a condition of approval, the FDA is requiring the manufacturer of elagolix to conduct a post marketing study on safety outcomes associated with co-administration of a combined oral contraceptive with elagolix.[68]

While BMD loss is a well-recognized side effect of elagolix, the FDA unexpectedly added three months to its elagolix review timeline due to questions related to liver function tests.[36] Liver toxicity was not reported in the Phase II and III trials of elagolix, but elevated liver function tests data are included in the FDA prescribing information. In addition, the prescribing information mentioned one death due to suicide in a patient treated with elagolix as well as four reports of suicidal ideation among the 2,090 women who were exposed to elagolix during Phase II and III studies. While the death was reported in the publication of the Phase III trials, information related to suicidal ideation was not available in any publication or presentation that we could identify.[16]

3.4 Summary and Comment

Using the ICER Evidence Matrix (Figure 3.1), we assigned evidence ratings for elagolix relative to alternative therapies for endometriosis-associated pain (Table 3.12).

Figure 3.1. ICER Evidence Rating Matrix



A* = *"Superior" *- High certainty of a substantial (moderate-large) net health benefit*
B* = *"Incremental" *- High certainty of a small net health benefit*
C* = *"Comparable" *- High certainty of a comparable net health benefit*
D* = *"Negative" *- High certainty of an inferior net health benefit*
B+* = *"Incremental or Better" *- Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit*
C+* = *"Comparable or Better" *- Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit*
P/I* = *"Promising but Inconclusive" *- Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit*
C-* = *"Comparable or Inferior" *- Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior*
I* = *"Insufficient" *- Any situation in which the level of certainty in the evidence is low*

Table 3.12. ICER Ratings on the Comparative Net Health Benefit of Elagolix*

Intervention	Comparator	ICER Evidence Rating
Elagolix	Placebo	P/I
	GnRH agonists	I
	Hormonal Treatments	I
	Aromatase Inhibitors	I

* These ratings were made prior to FDA approval of elagolix.

Elagolix versus Placebo

Compared to placebo, Phase III trials of elagolix (EM-I and EM-II) demonstrated a dose-response effect for dysmenorrhea and nonmenstrual pelvic pain at the two doses of elagolix with statistically significant improvements at three and six months for both doses. In Phase II trials, three months of treatment with elagolix versus placebo led to statistically significant decreases in dysmenorrhea but not nonmenstrual pelvic pain. Secondary pain and quality of life outcomes also demonstrated greater improvement for elagolix compared to placebo. Though use of rescue analgesics decreased more for elagolix compared to placebo, change in opioid use was similar, except at the highest dose of elagolix studied.

Limitations pertaining to outcomes reported in these trials include using a four-point scale to assess pain symptoms (B&B) that is not a true pain scale, was modified for use as a daily measure between the Phase II and III trials, and has no validated clinically meaningful difference. Moreover, the Phase III trials used novel primary outcomes, which consisted of composite measures of a clinical response for either dysmenorrhea or nonmenstrual pelvic pain using the B&B and stable or reduced analgesic use. Clinical response thresholds were defined for each Phase III trial for dysmenorrhea and NMPP. These primary composite outcomes had never been used previously and the individual components were not reported separately, limiting our ability to compare the Phase III results for elagolix to other trials or therapies.

Adverse effects of elagolix were consistent with a dose-dependent hypoestrogenic effect. Though adverse effects were more common with high-dose elagolix (200 mg BID) compared to placebo, few patients discontinued therapy due to adverse side effects in the trials. Nevertheless, potential serious adverse effects such as increased bone loss and changes in cholesterol levels were noted with elagolix compared to placebo. The long-term comparative safety of elagolix is uncertain, and reversal of bone loss and dyslipidemia following discontinuation of elagolix have not been fully evaluated to date. Furthermore, FDA prescribing information includes new information about

abnormally elevated markers of liver function and suicidal ideation in patients treated with elagolix.[16,36]

Consequently, despite evidence for improved pain symptoms with elagolix, the possibility of net harm cannot be ruled out at this time. We therefore judge the evidence to be "promising but inconclusive" for the comparison of elagolix to placebo ("P/I").

Elagolix versus GnRH Agonists, Hormonal Contraceptives, and Aromatase Inhibitors

For the comparisons of elagolix versus GnRH agonists, elagolix versus hormonal contraceptives, and elagolix versus aromatase inhibitors, we identified insufficient evidence with which to rate the net health benefit of elagolix. Although our literature review identified two head-to-head trials of elagolix versus leuprorelin acetate and depot medroxyprogesterone, respectively, several aspects of the design of these studies limit our ability to judge the comparative effectiveness of each regimen. The Phase II trials informing these comparisons were of fair quality, included small sample sizes, and enrolled patients who may not be representative of the population of women in the United States potentially eligible for therapy with elagolix. Moreover, statistical comparisons for efficacy and safety endpoints between active arms were limited, and the 200 mg twice daily dose of elagolix from the Phase III trials was not assessed. Due to the short duration of therapy in both head-to-head studies, important questions about the comparative safety of these therapies in terms of hypoestrogenic adverse side effects including reduced bone loss were not adequately addressed. Finally, no consistent significant benefit across outcome measures and comparators was observed in these head-to-head trials.

For the comparison of elagolix versus aromatase inhibitors, we did not identify any head-to-head evidence; a lack of comparative data, as well as differences in patient characteristics, common comparators, and outcome measurement precluded even indirect comparison through network meta-analysis. Thus, in consideration of the limited, short-term evidence for these comparisons, as well as the need to resolve critical questions around safety, we deem there to be insufficient ("I") evidence with which to judge the net health benefit of elagolix versus GnRH agonists, hormonal contraceptives, and aromatase inhibitors.

4. Long-Term Cost Effectiveness

4.1 Overview

The primary aim of this analysis was to estimate the cost-effectiveness of elagolix, an oral gonadotropin-releasing hormone (GnRH) antagonist, for the treatment of endometriosis-associated pain in adult, pre-menopausal women. Quality-adjusted survival and health care costs were estimated for elagolix and comparator treatment using a health care sector perspective. The target population age ranged between 32 and 50 years, starting from the average age of treatment initiation[24] and concluding at the average age of menopause.[37] The cost-effectiveness of elagolix was compared to *no active treatment* (i.e., placebo with non-specific rescue analgesics) due to differences between the elagolix evidence and other active treatment evidence in trial design, outcome measurement, age of cohort, and other factors highlighted in Section 3. For both elagolix and no active treatment, failure to respond (i.e., reduction in pain and use of analgesics) was modeled with subsequent lines of therapy, namely surgeries and add-back therapy.

Costs and outcomes were discounted at 3% per year. Incremental costs and outcomes were calculated comparing the intervention to its comparator. The model was developed in Microsoft Excel 2016 (Redmond, WA). The model framework and assumptions are described in detail below.

4.2 Methods

Model Structure

The decision analytic model structure was informed by the primary aim, previous modeling evidence, Phase III clinical trials for elagolix, and stakeholder input. The model included a short-term decision tree and a long-term Markov model to evaluate the cost-effectiveness of elagolix compared to no active treatment for the management of pain associated with endometriosis. Consistent with the duration of the pivotal clinical trial, the decision tree calculated the costs and consequences of six months of treatment with elagolix, including pathways relevant to short-term outcomes, such as response to treatment (i.e. pain reduction).[24] Long-term clinical outcomes, such as pain recurrence, surgeries (laparoscopy and hysterectomy), cardiovascular disease, and fractures were assessed via a Markov model. In the long-term Markov model, patients transitioned between endometriosis pain-related health states during three-month cycles over the model time horizon. A cycle length of three months was chosen because the lowest denomination of response was three months for elagolix and three months represents a reasonable time window for downstream modeled surgical procedures. The model time horizon is approximately 18 years, ending at 50 years of age, the average age of menopause onset (Figure 4.1).[37] Serious adverse clinical events were rarely observed within the randomized controlled trials and therefore were not emphasized within

the decision-tree. Long-term elagolix and comparator exposure, and the corresponding associations with adverse events such as fracture risk and cardiovascular disease, were included in the model using the best available evidence on the rate of developing such events in women.

The intervention and comparator were evaluated in terms of the proportion of the target population with clinical response (i.e. pain reduction) at six months using a decision tree. Our draft evidence report for this review used stratified decision trees to inform two versions of the same Markov model; one specific to dysmenorrhea-related pain and the other to nonmenstrual pelvic pain, as these correlated measures were reported as separate outcomes in the clinical trials and there was no explicit way to aggregate their effects without access to patient-level data. However, during the draft report public comment phase, stakeholders strongly suggested combining response for dysmenorrhea and response for nonmenstrual pelvic pain into one combined response metric and thus one version of a decision tree and Markov model. This feedback has been integrated into this report. We calculated a weighted average of response based on an average menstrual cycle duration, which weights response by time spent in menstruation (i.e., 5/28 days on average, with variability in sensitivity analyses) within each model cycle length to account for response to pain with and without menstruation. For any given measurement day, patients' response is dictated by whether or not they are within or outside of the menstrual cycle. Not surprisingly, response under this weighting scheme is skewed towards non-menstrual pelvic pain given that the bulk of time is spent outside of menstruation.

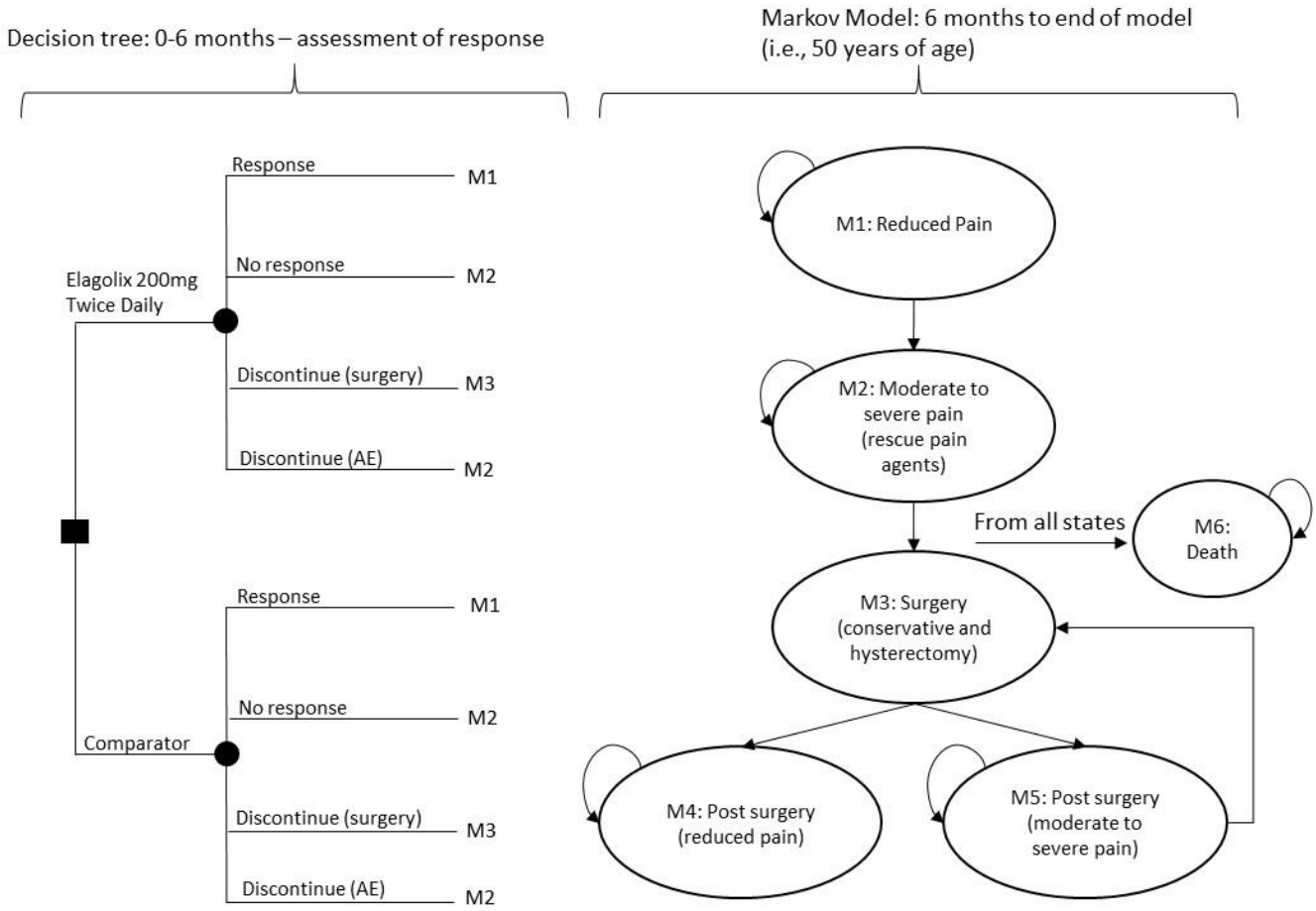
Menstruation duration was assumed the same between elagolix and no active treatment but was varied across a wide range in sensitivity analyses to account for uncertainty and variation. The combined response was used to assess long-run costs and outcomes of treatment with elagolix and the comparator. Combined response in the decision tree determined the initial state distribution of patients on elagolix and the comparator in the long-run Markov model.

Women who responded to treatment in the decision tree started in the reduced pain (M1) Markov model state and continued on their current therapy until discontinuation due to lack of efficacy. In the elagolix arm, we modeled a constant proportion of women to not incur costs of elagolix, which allowed for attempted and successful pregnancies during time off from treatment based on rates of pregnancies observed in the trial. Women who did not respond to treatment by six months in the decision tree started in the moderate-to-severe pain (M2) Markov model state where they were treated with rescue analgesics (e.g., NSAID, opioid). A small proportion of non-responders discontinued treatment with rescue analgesics in the decision tree and started directly in the surgery (M3) Markov health state at the end of six months. Women could continue in the moderate-to-severe pain state (M2) until opting for surgery.

After surgery, the model was flexible and allowed for a proportion to respond with reduced pain (M4) and for the remaining proportion to not respond to surgery (M5). Because a repeat and final surgery (i.e., hysterectomy and bilateral oophorectomy) could occur, the model accounted for

women who potentially responded to final surgery with reduced pain or those who did not respond to final surgery and continued with moderate-to-severe pain. Women in M1 and M4 incurred costs for analgesics at half the cost (assumed) of those in the M2, M3, and M5 states. This assumption supports the clinical trial evidence that pain management utilization is likely higher and perhaps twice as high in the moderate-to-severe pain state as compared to the reduced pain state with or without elagolix treatment. Additionally, a proportion of women in all post-surgery states were assumed to incur the cost of leuprolide and combined oral contraceptive add-back therapy based on prior evidence of add-back therapy use[69]. Death (M6) could occur from any state in the model as an all-cause death risk, with the exception of an additional death risk for those undergoing a hysterectomy. Model outcomes included cost, life years, quality-adjusted life years (QALYs), and rates of surgeries (laparoscopy and hysterectomy), cardiovascular disease, and fractures over the time horizon.

Figure 4.1. Model Framework



Target Population

The population of focus for this review was adult premenopausal women with symptomatic endometriosis and moderate-to-severe associated pain. Characteristics of the modeled population were aggregated (i.e., as weighted averages) from the elagolix clinical trials (EM-I and EM-II) and are shown in Table 4.1.

Table 4.1. Base Case Model Cohort Characteristics (Aggregate of EM-I and EM-II for Placebo and Elagolix 200 mg Twice Daily)

Cohort Characteristic	Value	Source
Median Age	32 (18-48) years	Taylor et al., 2017[24]
Body Mass Index	28 ± 6.2	Taylor et al., 2017[24]
Score for Dysmenorrhea [0 (None) – 3 (Severe)]	2.2 ± 0.5	Taylor et al., 2017[24]
Score for Nonmenstrual Pain [0 (None) – 3 (Severe)]	1.6 ± 0.5	Taylor et al., 2017[24]
Score on Numeric Rating Scale [0 (None) – 10 (Worst)]	5.5 ± 1.7	Taylor et al., 2017[24]

Treatments

Intervention

The intervention selected for the model was chosen based on input from patient organizations, clinicians, and payers on which regimen to include. We focused on elagolix dosed at a strength of 200 mg twice daily because it showed the greatest reductions in pain and stable use of rescue analgesic agents in the Elaris EM-I and EM-II trials.

Comparator

The comparator of interest was no active treatment. As noted in Section 3 and above, severe limitations on the applicability of small trials comparing elagolix to other active agents, and limitations on the broader evidence base preventing indirect comparisons, restricted the comparator to that used in the elagolix Phase III trials.

Key Model Characteristics, Choices and Assumptions

The base case analysis took a health system perspective and focused on direct medical care costs only. Outcomes were estimated until 50 years of age, the average age of menopause onset, to capture the potential lifetime impacts of short-term and ongoing treatment with elagolix and pain management. The time horizon was based on the proposed mechanism of action of elagolix, inducing a hypo-estrogenic state, which occurs with natural menopause at around 50 years of age

for the average woman. Costs and outcomes were discounted at 3% per year. Model choices and assumptions are described in Table 4.2.

Table 4.2. Key Model Assumptions

Assumption	Rationale
Patients not responding to treatment with elagolix after the first six months in the decision tree were not re-treated with elagolix and moved directly to treatment with pain agents and/or surgical procedures.	Re-treatment with elagolix was not attempted for women who did not respond in clinical trials. The re-treatment efficacy of elagolix is unknown.
Endometriosis-related treatment had no direct effect on mortality.	There was no direct evidence linking treatment to decreased mortality.
The proportion of patients responding to treatment in the decision tree model continued on treatment until discontinuation due to lack of efficacy with recurrence to moderate-to-severe pain immediately following discontinuation in the Markov model.	Women responding to treatment stayed on treatment to avoid pain recurrence.
Transition probabilities for discontinuation due to lack of efficacy differed by treatment arm (i.e., elagolix and comparator) but did not vary over time.	There was no available evidence on time-varying discontinuation rates for elagolix.
A constant proportion of women on elagolix each cycle was assumed to be off treatment for attempted and successful pregnancies.	Trial evidence showed women discontinued to attempt pregnancy, but there was no evidence suggesting they would permanently discontinue treatment post-delivery.
Two time-horizons were estimated to reflect short-run (six months) and long-run (18 years) use of elagolix.	Treatment duration and response longer than six months is unknown with GnRH agonists or antagonists; however, clinical practice experts suggest the use of these agents may continue past label indications of six months to one year if the patient responds well to therapy.
Women passing through the surgery state incurred a disutility from surgery in addition to the disutility of moderate-to-severe pain during the surgery time cycle.	Evidence suggested there was a temporary quality of life decrement related to surgery, above and beyond moderate-to-severe pain.
Women in post-hysterectomy health states incurred a disutility from the loss of fertility for the remainder of the model time horizon.	Evidence suggested there was a decrement to quality of life related to the loss of fertility.
Women responding and staying on elagolix were assumed to have a constant increased risk for cardiovascular disease and fracture risk as compared to those on no active treatment.	Trial evidence suggested changes in lipid panels and bone mineral density might increase the risk of cardiovascular disease and fractures as compared to age-matched peers not on elagolix.
All states included the cost for treating a proportion of women on NSAID and opioid therapy for pain management. The cost incurred in the pain reduced states is assumed half of the cost of NSAID and opioid therapy use in moderate-to-severe pain health states.	This assumption supports the clinical trial evidence that pain management utilization is likely higher and perhaps twice as high in the moderate-to-severe pain state as compared to the reduced pain state with or without elagolix add-on treatment.

A discount of 27% off the wholesale acquisition cost (WAC) of elagolix was assumed.	A discount off of the WAC of elagolix is expected; however, due to the recent approval of elagolix, an average discount was not able to be estimated using the SSR Health database. Therefore, we assumed a discount of 27% because that is the average discount across all branded pharmaceuticals.
Weighted average combined response to elagolix and no active treatment was assumed for the base case analysis. Specifically, response to dysmenorrhea trial evidence was applied to an average proportion of time of menstruation within each model cycle equal to 5/28. Response to nonmenstrual pelvic pain was applied to the remaining proportion of time (1- 5/28) within each model cycle. Menstruation duration was assumed the same between elagolix and no active treatment.	Trial evidence did not report a combined response metric for dysmenorrhea and nonmenstrual pelvic pain. The combined response assumption weights response by time spent in menstruation within each model cycle length to account for response to pain with and without menstruation. This measure is reflective of not requiring all days to achieve response, but on any selected day. Given that most of the patient's time is spent in a nonmenstrual state, this weighted average is closer to the nonmenstrual pelvic pain treatment response rates.

Model Inputs

Clinical Inputs

Treatment Response

Treatment response rates were obtained from published literature and information provided from the manufacturer. The initial response rates used in the short-term decision tree are provided in Table 4.3.

Table 4.3. Treatment Response Rates (Aggregate of EM-I and EM-II Trials through Six Months)

	Elagolix 200 mg Twice Daily	No Active Treatment*	Source
Response At 6 Months [Dysmenorrhea]	76.1%	24.2%	Taylor et al., 2017[24]
Response At 6 Months [Nonmenstrual Pelvic Pain]	62.1%	37.7%	Taylor et al., 2017[24]
Absolute Difference in Response to Dysmenorrhea vs. No Active Treatment	52.4% (46.9%, 56.8%)	Referent[a]	Calculated field
Absolute Difference in Response to Nonmenstrual Pelvic Pain vs. No Active Treatment	24.8% (19.1%, 30.3%)	Referent[a]	Calculated field
Weighted Average Combined Response (Dysmenorrhea and Nonmenstrual Pelvic Pain)	65.6%	35.3%	Calculated field assuming % time for menstruation = 5/28 days
Absolute Difference in Weighted Average Response vs. No Active Treatment	27.6%	Referent[a]	Calculated field
Proportion Who Discontinued Due to Adverse Events	9.6%	6.0%	Taylor et al., 2017[24]
Discontinuation Due to Adverse Events Risk Ratio for Elagolix vs. No Active Treatment	1.61 (1.08, 2.39)	Referent[a]	Calculated field
Proportion Who Discontinued Due to Surgery	0.6%	1.4%	Taylor et al., 2017[24]
Discontinuation Due to Surgery Risk Ratio for Elagolix vs. No Active Treatment	0.46 (0.13, 1.66)	Referent[a]	Calculated field

[a]Inputs not varied were due to the input's contribution to a comparative model estimate, which was varied within sensitivity analyses using 2.5 and 97.5 percentiles of evidence-based probability distributions.
*No Active Treatment refers to placebo response in the EM-I and EM-II trials

Inputs to inform the transition probabilities between the Markov model health states are detailed in Table 4.4. All transition probabilities in Table 4.4 are assumed as fixed likelihoods throughout the time horizon of the Markov model. These probabilities were obtained from published literature and information provided by the manufacturer. Probabilities of key adverse events, including risk of fracture and risk of overt cardiovascular disease, are available in Appendix Table F3.

Table 4.4. Transition Probabilities and Risk Ratios for Markov Model

Input parameter	Value[a]	Lower	Upper	Source
Probability of Pain Recurrence (Discontinue Due to Lack of Efficacy): Elagolix 200 Mg Twice Daily (Responders)[b]	0.0031	Not varied		Taylor et al., 2017[24]
Probability of Pain Recurrence (Discontinue Due to Lack of Efficacy): No Active Treatment* (Responders)[b]	0.0104	Not varied		Taylor et al., 2017[24]
Pain Recurrence (Discontinuation Due to Lack of Efficacy) Risk Ratio for Elagolix vs. No Active Treatment	0.30	0.08	1.06	Calculated field
Proportion of Women on Elagolix Treatment	0.981	0.83	1.0	Assumed based on placebo arm evidence of discontinuation due to pregnancy
Probability of Subsequent Surgery (Conditional on Prior Surgery)[b]	0.0260	0.017	0.037	Soliman et al., 2016[70]
Probability of Hysterectomy (Conditional on Prior Surgery) [b]	0.0164	0.009	0.026	Soliman et al., 2016[47]
Probability of Response to Subsequent Surgery[b]	0.4377	Not varied		Soliman et al., 2016[47]
Probability of Response to Hysterectomy[b]	0.4970	Not varied		Soliman et al., 2016[47]
Proportion Who Discontinued for Pregnancy	0.0190	0	0. 17	Taylor et al., 2017[24]
Probability of Death from Hysterectomy Surgery[b]	0.0080	0.004	0.012	Mäkinen et al., 2001[71]

[a]Input parameters will be varied in sensitivity analyses using 2.5 and 97.5 percentiles of evidence-based probability distributions unless otherwise stated. Inputs not varied were due to the input's contribution to a comparative model estimate, which was varied within sensitivity analyses.
[b]3-month cycle length probabilities
*No Active Treatment refers to placebo response in the EM-I and EM-II trials

Utility Inputs

Model Health States

To measure quality of life, utilities were applied to each model health state. Health state utilities were derived from published literature and applied to the disease states. While utilities differed by health states, they remained consistent within a health state across different treatments. The utilities for each model health state are presented in Table 4.5. To calculate the mean utility for the moderate-to-severe pain health state, we relied on a mapping function between the numerical pain rating scale and the EQ-5D.[72] Baseline numerical pain rating scores were consistent across treatment arms in EM-I and EM-II, and therefore served as a baseline pain level for the modeled population.[24] Disutilities from surgical procedures were applied to those experiencing moderate-to-severe pain only during duration when the surgery occurs. A disutility related to the loss of fertility was applied to both subsequent health states post-hysterectomy for women who underwent this surgery, for the remainder of the model. Details on disutilities associated with cardiovascular disease and fractures can be found in Appendix F, Table F4.

Table 4.5. Model Health State Utilities

Health State	Utility	Lower	Upper	Source
Mean EQ-5D Health Utility for Women in The United States Without Pain	0.92	0.916	0.924	Sullivan et al., 2006[73]
Moderate-To-Severe Pain Health State	0.73	0.703	0.756	Dixon et al., 2011[72]
Surgical Disutility (E.G., Laparoscopy)	-0.06	-0.031	-0.085	Ganz et al., 2013[74]
Surgical Disutility (Hysterectomy)	-0.07	-0.038	0.103	Ganz et al., 2013[74]
Loss of Fertility Disutility (All Subsequent Post-Hysterectomy Health States)	-0.07	0.039	0.107	Ganz et al., 2013[74]

[a] Utility inputs are varied in sensitivity analyses

Economic Inputs

Drug Acquisition Costs

We used Redbook[38] to identify WACs for pain rescue agents. A discount of 27%, the average discount across all branded pharmaceuticals, from the WAC was assumed for elagolix.[39] The annual WAC and assumed annual net price for elagolix were $10,138 and $7,400, respectively. Discounts and rebates were not assumed for generic drugs. Other drug cost inputs include Naproxen sodium (550 mg once daily) at $2.58 per pill and Hydrocodone in Acetaminophen (10 mg hydrocodone/325 mg acetaminophen twice daily) at $0.90 per pill. Threshold prices for elagolix were also calculated

at the three cost-effectiveness thresholds ($50,000 per QALY gained, $100,000 per QALY gained, and $150,000 per QALY gained).

Productivity Costs

Lost productivity was included to estimate cost-outcomes from a modified societal perspective as a scenario analysis (Table 4.6). An average hourly wage and hours of work missed per cycle were allocated to the proportion of women in moderate-to-severe pain health states for each treatment arm using literature-based sources.[41,75] Specifically, Soliman et al. reported presenteeism and absenteeism by the number of pain symptoms occurring among women with endometriosis.[41] For women with two symptoms (e.g., dysmenorrhea and nonmenstrual pelvic pain), the self-reported mean number of hours per week of absenteeism and presenteeism was 7.8 hours as compared to 2.2 hours for those experiencing zero symptoms. Over a 3-month cycle length, women experiencing two symptoms have approximately 67 hours (7.8 hours*4 weeks*3 months – 2.2 hours*4 weeks*3 months) of additional absenteeism and presenteeism over women with zero symptoms.

Table 4.6. Societal Perspective Inputs

Category	Value	Source
Average Hourly Wage	$24.34 per hour	United States Department of Labor Bureau of Labor Statistics, 2017[75]
Difference in Presenteeism and Absenteeism Hours Between Severe Pain and No Pain Per 3-Months	67.2 hours	Soliman et al., 2017[41]

Other Costs

Our model included cost of health care resources used such as laparoscopic surgery, hysterectomy, physician office visits, and adverse events-related costs, details of which can be found in Appendix F Tables F2 and F5.

Sensitivity Analyses

We conducted one-way sensitivity analyses to identify the key drivers of model outcomes, using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges for each input described in the model inputs section above. Probabilistic analyses were performed by jointly varying all model parameters over 5,000 simulations, then calculating 95% credible range estimates for each model outcome based on the long-run time horizon results. Additionally, we conducted a threshold analysis by systematically altering the price of the intervention to estimate the maximum prices that would correspond to commonly-cited willingness to pay (WTP) thresholds.

Scenario Analyses

Given available evidence on patient health-state level costs and lost productivity to the patient and caregiver, the perspective was expanded to a modified societal one. As referenced previously, the draft report used stratified decision trees to inform separate model versions by dysmenorrhea and nonmenstrual pelvic pain. To address multiple scenarios around response definitions, we performed additional response-specific scenario analyses. First, we assessed response as if it was alternatively to dysmenorrhea pain only or nonmenstrual pelvic pain only (see Table 4.3). In addition, we received unpublished data from AbbVie, subsequent to our decision to use the weighted approach described above, on the proportion of women in the elagolix trials who responded on both the dysmenorrhea and nonmenstrual pelvic pain scales.[28] Specifically, in a post-hoc analysis of pooled data from elagolix phase III trials, 56.41% of women on elagolix 200 mg twice daily responded to both dysmenorrhea and nonmenstrual pelvic pain versus 17.19% in the comparator group (placebo), an approximate 40% absolute difference between groups. We conducted a scenario analysis using these data to ascertain how the results differed from our revised base case. The response to both dysmenorrhea and nonmenstrual pelvic pain provided by AbbVie can be thought of as a measure of "full response" where women are responding during and outside of their menstrual cycle; whereas the base case analysis assumed a response reflective of the type of response on any selected day.

Finally, a threshold analysis was conducted to determine the elagolix price needed to achieve value-based price benchmarks of $50,000, $100,000, and $150,000 per QALY gained, using the base case deterministic inputs and assumptions, for the next version of this report.

Model Validation

We used several approaches to validate the model. First, we shared our methods and preliminary results with manufacturers, patient groups, and clinical experts, requesting their feedback. Based on feedback from these groups, we refined data inputs used in the model, as needed. Second, we varied model input parameters to evaluate face validity of changes in results. We performed model verification for model calculations using reviewers. Finally, we compared results to other cost-effectiveness models in this therapy area.

4.3 Results

Long-Run Clinical Outcomes

Table 4.7 indicates the long-run clinical outcomes for response to treatment. This analysis only reported the outcomes for different surgery types (laparoscopy, hysterectomy), cardiovascular disease cases, and fractures. In both cohorts, elagolix resulted in fewer surgeries relative to no

active treatment. Long-term risks of cardiovascular disease and fractures were not materially different between elagolix and no active treatment.

Table 4.7. Long-Run Clinical Outcomes (18-year time horizon)

Outcome (per 1,000 women)	Elagolix 200 mg Twice Daily	No Active Treatment	Incremental
Surgeries (e.g., Laparoscopy)	368	647	-279
Surgeries (Hysterectomy)	94	169	-75
Cardiovascular Disease Cases	16.5	15.9	0.6
Fractures	0.92	0.08	0.84

Base Case Results

Quality adjusted life years (QALYs) as well as the total discounted costs within six months and an 18-year time horizon are detailed in Table 4.8.

Elagolix 200 mg twice daily had a total undiscounted cost of approximately $4,300 with 0.43 QALYs at six months and a total discounted cost of approximately $79,800 and 11.77 QALYs at 18 years. This contrasted with the comparator population (i.e. no active treatment), which had a total undiscounted cost of approximately $700 with 0.40 QALYs and a total discounted cost of approximately $26,000 with 11.11 QALYs at six months and 18 years, respectively.

Table 4.8. Results for the Base Case Discounted Costs and Outcomes from the Model

Intervention	Intervention Costs*	Non-Intervention Costs§	Total Costs	QALYs
Short-Run Results (6 Months)‡				
Elagolix 200 mg Twice Daily¶	$3,800	$500	$4,300	0.43
No Active Treatment	$100	$600	$700	0.40
Long-Run Results (18-Year Time Horizon)				
Elagolix 200 mg Twice Daily¶	$64,300	$15,400	$79,800	11.77
No Active Treatment	$6,000	$20,000	$26,000	11.11

QALY: Quality-Adjusted Life Year
*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 no active treatment 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
All costs rounded to the nearest $100

Base Case Incremental Results

Table 4.9 presents the incremental results from the base case analysis, specifically cost per QALY gained versus no active treatment measured in the short-run and in the long-run variation.

Cost per QALY gained for elagolix versus no active treatment was approximately $126,800 and $81,000 for short-run and the long-run time-horizons, respectively.

Table 4.9. Base Case Discounted Incremental Results

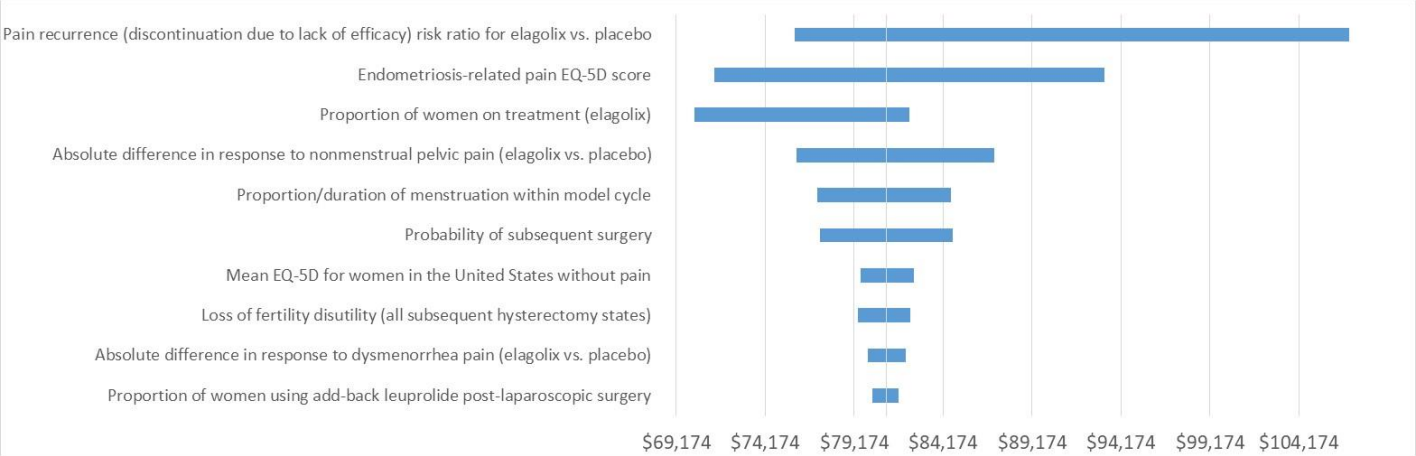
Intervention	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio (vs. No Active Treatment)
Elagolix 200 mg twice daily *short-run*	$3,600	0.028	$126,800
Elagolix 200 mg twice daily *long-run*	$53,700	0.663	$81,000

QALY: Quality-Adjusted Life Year
All costs rounded to the nearest $100
Incremental Cost effectiveness Ratios rounded to the nearest $1,000

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY for results. Inputs that had the biggest impact on cost-effectiveness ratios include the endometriosis-related pain EQ-5D score, probability of pain recurrence (discontinuation due to lack of efficacy) for elagolix versus no active treatment, and proportion of women on treatment (Figures 4.2 and Appendix F, Table F6). The probabilistic analysis results indicate a relatively high likelihood of achieving thresholds for cost-effectiveness between $100,000 and $150,000 per QALY gained (Table 4.10).

Figure 4.2. Tornado Diagram(s) for One-Way Sensitivity Analyses of Elagolix versus No Active Treatment – Long-Run Time Horizon



Base case incremental cost-effectiveness ratio: $81,000 per QALY gained.

Table 4.10. Probabilistic Sensitivity Analysis Results: Elagolix versus No Active Treatment

Proportion of Simulations That Were Cost-Effective			
	Cost-Effective at $50,000 per QALY	**Cost-Effective at $100,000 per QALY**	**Cost-Effective at $150,000 per QALY**
Elagolix 200 mg Twice Daily ***Long-Run***	0.10%	94.74%	99.68%

QALY: Quality-Adjusted Life Year

Scenario Analyses Results

Modified Societal Perspective

The base case health sector perspective was expanded to a restricted societal perspective to account for potential patient-level lost productivity costs over the time horizon. Cost-effectiveness ratios were reduced from including potential lost productivity estimates as compared to base case cost-effectiveness ratios (Table 4.11).

Table 4.11. Incremental Results for Modified Societal Perspective in the Long-Run Time Horizon

	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio
Elagolix 200 mg Twice Daily vs. No Active Treatment	$32,400	0.663	$48,900

QALY: Quality-Adjusted Life Year
All costs rounded to the nearest $100
Incremental Cost effectiveness Ratios rounded to the nearest $1,000

Response Definition Scenario Analyses

The response definitions were separated and combined using the trial-reported definitions of response (see Table 4.3 for separate response inputs). Table 4.12 displays the incremental costs, incremental QALYs, and cost effectiveness ratio per QALY for the three respective response definitions over the long-run time horizon. Using response to dysmenorrhea only (76.1% elagolix vs. 24.2% no active treatment), the cost-effectiveness ratio was more favorable than the base case estimate. Using response to nonmenstrual pelvic pain only (62.1% elagolix vs. 37.7% no active treatment), the cost-effectiveness ratio slightly increased as compared to the base case estimate (which was weighted toward response to this type of pain). Finally, using combined response for women who responded to both dysmenorrhea and nonmenstrual pelvic pain (56.41% elagolix vs. 17.19% placebo),[28] the cost-effectiveness ratio was more favorable than the base case estimate. The response to both dysmenorrhea and nonmenstrual pelvic pain can be thought of as a measure of "full response" where women are responding during and outside of their menstrual cycle, whereas the base case analysis assumed a response reflective of the type of response on any selected day. The response definition scenario analyses demonstrated that as incremental response to different or multiple pain symptoms increased from the use of elagolix relative to no active treatment, the cost-effectiveness ratios were reduced as compared to base case; conversely as incremental response to pain decreases, the cost-effectiveness ratios increased in relation to the base case.

Table 4.12. Response Definition Scenario Analyses

Response Definition	Incremental Costs	Incremental QALYs	Incremental Cost Effectiveness Ratio
Response to Dysmenorrhea Only (Elagolix 200 Mg Twice Daily Vs. No Active Treatment)	$60,400	1.04	$58,000
Response to Nonmenstrual Pelvic Pain Only (Elagolix 200 Mg Twice Daily Vs. No Active Treatment)	$52,300	0.58	$90,000
Response to Both Dysmenorrhea and Nonmenstrual Pelvic Pain (Elagolix 200 Mg Twice Daily Vs. No Active Treatment)	$45,600	0.78	$58,000

QALY: Quality-Adjusted Life Year
All costs rounded to the nearest $100
Incremental Cost effectiveness Ratios rounded to the nearest $1,000

Threshold Analyses Results

Tables 4.13 presents the threshold annual price results at $50,000, $100,000, and $150,000 per QALY for within-trial and long-run variations, as compared to no active treatment. The threshold analyses suggest what the price would need to be to reach the specific thresholds. Importantly, we note that the short-run timeline is now consistent with the FDA-approved duration of treatment with the 200 mg twice-daily dose of elagolix (six months); it is currently uncertain whether longer-term treatment (possibly with add-back therapy) will occur.

Table 4.13. Annual Threshold Price Results

Intervention	Annual Price at $50,000 per QALY	Annual Price at $100,000 per QALY	Annual Price at $150,000 per QALY
Elagolix 200 mg Twice Daily *Short-Run**	$2,900	$5,800	$8,400
Elagolix 200 mg Twice Daily *Long-Run*	$4,700	$8,800	$12,800

*Represent 6 months duration, as seen in the trials
QALY: Quality-Adjusted Life Year
All prices rounded to the nearest $100

Model Validation

Model validation followed standard practices in the field. All mathematical functions were consistent with the report (and supplemental Appendix materials). Sensitivity analyses with null input values produced findings consistent with expectations.

We searched the literature to identify models that were similar to our analysis, with comparable populations, settings, perspective, and treatments. We found no published economic evaluations of elagolix in women with moderate-to-severe endometriosis related pain. Our review of all other models thus focused more on comparing modeling methodologies and less on results. We reviewed only those models that included current treatments, were developed in the last 10 years, and were similar to our model from a setting and population perspective.

A model developed by NICE compared current endometriosis treatments, including pain rescue agents, hormone replacement therapy, GnRH agonists and antagonists, and surgery, in different populations, one of which was UK women with endometriosis where pain was the main symptom.[76] Incremental QALYs with elagolix in the ICER model (0.663) align with the NICE model's incremental QALYs with laparoscopy + hormonal therapy (0.748) versus no treatment. However, these incremental QALY gains aren't comparable owing to differences in modeling methodologies between the two models. i) The NICE model begins with women with no diagnosis of endometriosis; patients could cycle through being undiagnosed and treated, diagnosed and untreated, or diagnosed and treated before ending in either menopause or death. The ICER model only includes patients indicated for treatment with elagolix, thus focusing on our decision problem for this review. ii) The NICE model employs a time-horizon, in that the model simulates women based on when they attain menopause or die, unlike the ICER model, which ends at assumed fixed age of menopause based on clinical data in this disease area. iii) The NICE model simulates diagnosis of endometriosis through empirical diagnosis as well as diagnostic laparoscopy, unlike the ICER model where the target population of women with endometriosis have been definitively diagnosed laparoscopically. iv) While both models incorporated a fertility-associated disutility, the ICER model includes the utility only post-hysterectomy, while the NICE model incorporates this disutility in all women who aren't able to conceive. v) While both the ICER and NICE model have similar utilities for women in the healthy state (0.92 vs. 0.91), the ICER model estimates higher utilities to women with diagnosed endometriosis relative to the NICE model (0.73 vs. 0.68).

A model by Sanghera et al. assessed the cost-effectiveness of hormonal treatment relative to 'no treatment' in women previously treated with conservative surgery for endometriosis, in the UK.[77] A key difference between both models is health state utility derivation. While the ICER model sourced utility estimates from the published literature and employed a mapping function to obtain the utility estimate for the "Moderate-to-Severe Pain" state, Sanghera et al. relied on clinician input to estimate utilities for the endometriosis treatments in their model. Symptomatic patients in their model had utilities ranging from 0.25 to 0.3 based on type of non-surgical treatment, which is

substantially lower than the 0.73 estimate the ICER model used in patients with moderate-to-severe endometriosis-related pain. Other differences between the models include: ii) Sanghera et al. modeled treatment duration such that all non-surgical, non-device treatments could be discontinued in asymptomatic women if women were asymptomatic for at least six months, unlike the ICER model where women in the "Reduced Pain" state continued elagolix until treatment efficacy waned such that these women reverted to the "Moderate-to-Severe Pain" state. iii) Sanghera et al.'s model used one-month cycle-length unlike the ICER model's three-month cycle length and used a three-year time-horizon in keeping with the time-horizon of a then planned RCT, unlike the ICER model's longer time-horizon. Sanghera et al. did not include background mortality in their model due to the short time-horizon they used, unlike the ICER model, where background mortality was included. iv) While both models allowed for conservative surgery and hysterectomy if previous non-surgical treatments failed, Sanghera et al. allowed for surgery conditioned on two sets of prior hormonal treatment, unlike the ICER model.

A model by Wu et al. evaluated the cost-effectiveness of GnRH therapies (three and six months) and oral contraceptive therapy relative to no medical therapy for preventing endometriosis recurrence in women who underwent conservative surgery for endometriosis in China.[78] Like the ICER model, Wu et al.'s model had a time-horizon of approximately 18 years, beginning at age 32 years and ending at menopause (approximately 50 years). Total QALYs accrued for interventions differed between both models, with elagolix in the ICER model accruing 11.77 QALYs, and the active interventions in the Wu et al. model accruing between 7.09 and 7.69 QALYs across the different types of endometriosis. Key differences between Wu et al.'s model and the ICER model include: i) Inclusion of an ovarian cancer state in Wu et al.'s model due to evidence on the increased risk of ovarian cancer in women with endometriosis. The ICER model did not include ovarian cancer as a downstream complication in the disease pathway primarily because it didn't fit the decision problem, and secondarily, we found no evidence on a differential risk of this complication in women with endometriosis using elagolix compared to those who did not. ii) Wu et al. used health state utilities reported in Sanghera et al.'s model, which were elicited from clinical expert opinions and not the published evidence used in the ICER model. iii) Wu et al. assumed six months of GnRH agonists post repeat-surgery to prevent further recurrence based on clinical expert opinion, while the ICER model did not make this assumption due to lack of robust data on the use of GnRH agonists post elagolix or repeat surgery.

4.4 Summary and Comment

The base case findings from our analysis suggest that the use of elagolix to treat moderate-to-severe endometriosis-related pain provides clinical benefit in terms of gains in health-related quality of life relative to no active treatment. This translated into cost-effectiveness estimates that were under the upper bound of the commonly-cited cost-effectiveness threshold of $150,000 per QALY gained in the selected endometriosis cohort under the assumptions used in this analysis. We

note, however, that the only comparison available because of data limitations was to no active medical management beyond analgesic agents (i.e., placebo with non-specific rescue analgesics), which is an unrealistic clinical strategy in women with moderate-to-severe endometriosis-associated pain. However, the model did include downstream surgeries and add-back therapy within subsequent states for non-responders.

Costs per QALY gained versus no active treatment were approximately $126,800 and $81,000 for short-run and long-run time-horizons, respectively. The results were robust through one-way and probabilistic analyses given the parameter uncertainties. Although somewhat sensitive to definition of treatment response (e.g., weighted average response, response to both dysmenorrhea and nonmenstrual pelvic pain), the perspective of the analysis, and other model inputs, cost-effectiveness estimates remained less than $150,000 per QALY gained threshold.

Limitations

There were several important and distinctive limitations to our analysis. First and foremost, severe limitations in available data precluded any comparison to another active treatment such as GnRH agonists or oral contraceptives; such a comparison may have involved a very different calculus of elagolix's incremental costs, benefits, and risks. Furthermore, our analysis assumes treatment responders have reduced pain that is equivalent with that of the healthy population of women in the United States of a similar age. It is therefore likely that clinical benefits in our analysis are overstated to some extent, although the magnitude of this effect is unknown without comparable data. Further evidence on active comparators and directly elicited health utility scores from elagolix Phase III trial evidence could in fact validate or refute the model findings. We also modeled cost-effectiveness using an assumed discount off of the WAC, as the drug is newly FDA-approved and the actual net price is unknown. In addition, as highlighted in Section 7, a high price, even if felt to be value-based, has the potential to significantly strain health-system budgets given the high prevalence of this condition.

In addition, when searching for long-run clinical evidence on response and discontinuation, we were unable to find high quality evidence. No evidence currently exists on the long-term use or prescribing patterns of elagolix in the target population, with the current trial data pointing to only a short duration of use. Given the FDA's approval of the higher dose of elagolix for a six-month treatment duration, the length of a treatment course in typical clinical practice is currently unknown. Data and evidence used in the study was abstracted primarily from Phase III trials. However, we modeled the long-term treatment pathways that included different surgical interventions for elagolix and the comparator arms. Thus, consistent with common economic modeling practice, we are comparing the costs and outcomes of elagolix and its long-run surgical treatment options to that of a common standard of care alternative.

Available evidence from Phase III trials also contributed to our need to average response across type of pain. Response to dysmenorrhea and nonmenstrual pelvic pain were split in Phase III trials, yet are correlated outcomes, and cannot simply be averaged across response assessment. With no access to patient-level data, we calculated a weighted average of response based on an average menstrual cycle duration. Specifically, response to dysmenorrhea trial evidence was applied to an average proportion of time of menstruation within each model cycle. Response to nonmenstrual pelvic pain was applied to the remaining proportion of time within each model cycle to estimate an average combined measure of response. Given a lack of long-term data on menstruation duration, we assumed the same duration between elagolix and no active treatment. However, initial trial evidence suggested a significant proportion of women had amenorrhea (i.e., no menstruation) after six months on elagolix treatment at the 200 mg dose; our analyses may have therefore overestimated elagolix's clinical benefits given the more pronounced treatment effect on the dysmenorrhea scale.

To address our assumptions around averaged response to pain, we estimated scenario analyses to inform different response scenarios including women responding to dysmenorrhea only, nonmenstrual pelvic pain only, and women responding to both dysmenorrhea and nonmenstrual pelvic pain. The response to both dysmenorrhea and nonmenstrual pelvic pain can be thought of as a measure of "full response" where women are responding during and outside of their menstrual cycle; whereas the base case analysis assumed a response reflective of not requiring all days to achieve response, but on any selected day. The response definition scenario analyses demonstrated that as incremental response to different or multiple pain symptoms increased from the use of elagolix relative to no active treatment, the cost-effectiveness ratios were reduced as compared to base case; conversely as incremental response to pain decreases, the cost-effectiveness ratios increased as compared to base case.

Pain, as an outcome, was used to derive the quality of life effectiveness estimates for elagolix and no active treatment in the model. Health utilities for moderate-to-severe pain states were mapped from the numeric pain rating scale to the EQ-5D. These health utilities were initially derived from a United Kingdom population. This acts as a limitation due to the potential variance in demographics, preferences, and compositional make-up between populations.

Finally, probabilities used to forecast the long-term costs and outcomes were abstracted from the six-month trial evidence. Without evidence or biological plausibility to suggest otherwise, we assumed these event probabilities such as treatment success, discontinuation, and long-run adverse events were fixed over time (and consistent with the trial evidence probabilities). If future evidence suggests time-dependent probabilities, then this evidence may affect the long-term value findings. For example, the probability of recurrence (discontinuation due to lack of efficacy) was a significant driver of uncertainty in the results. In general, the one-way sensitivity analyses indicated as discontinuation rate increased for both elagolix and no active treatment, the cost-effectiveness of elagolix versus no active treatment worsened. Therefore, if discontinuation in clinical practice is

higher than in clinical trials, long-term value of using elagolix versus no active treatment will decrease. In addition, as FDA review has been extended to further examine liver function test findings, the extent to which the integration of any new safety signal affects our results is currently unknown.

Conclusions

In conclusion, the findings of our analysis suggest that the endometriosis therapy of focus for this review provides marginal increases in quality-adjusted survival over no active treatment. With the evidence available at this time, the estimated cost-effectiveness of elagolix 200 mg twice daily falls within the range of $50,000 to $150,000 per QALY gained.

5. Additional Considerations

Our reviews seek to provide information on 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 are listed in the table below, and the subsequent text provides detail about the elements that are applicable to the review of elagolix.

Table 5.1. Potential Other Benefits or Contextual Considerations (Not Specific to Any Disease or Therapy)

Potential Other Benefits
This intervention offers reduced complexity that will significantly improve patient outcomes.
This intervention will reduce important health disparities across racial, ethnic, gender, socio-economic, or regional categories.
This intervention will significantly reduce caregiver or broader family burden.
This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients for whom other available treatments have failed.
This intervention will have a significant impact on improving return to work and/or overall productivity.
Other important benefits or disadvantages that should have an important role in judgments of the value of this intervention.
Other Contextual Considerations
This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
This intervention is the first to offer any improvement for patients with this condition.
Compared to the comparators of interest, there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to the comparators of interest, there is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention.
There are additional contextual considerations that should have an important role in judgments of the value of this intervention.

5.1 Potential Other Benefits

Elagolix is the first GnRH antagonist to receive FDA approval for women with symptomatic endometriosis. While current evidence suggests GnRH antagonists work similarly to GnRH agonists and other hormonal treatments, the side effects of these treatments are known to differ. As a therapy that offers a novel mechanism of action, elagolix presents an alternative option to those women who do not find relief or suffer severe side effects from other regimens.

Due to its short half-life (approximately six hours), elagolix is taken daily as an oral formulation. This is likely to be viewed favorably by patients, as it may reduce healthcare complexity for women compared to GnRH agonists that are delivered via nasal spray or in-office intramuscular injections, or who are considering the potential for complications and time to recover from surgery. Reducing healthcare complexity and alleviating endometriosis-related pain may also improve productivity, which is negatively affected by a diagnosis of endometriosis.[8] Patients have indicated that frequent doctor's office visits in search of a diagnosis and symptom relief, in combination with debilitating pain, can necessitate spending significant time away from school or work.

Elagolix is most likely to be considered as an alternative to GnRH agonists. The most commonly used GnRH agonist, leuprorelin acetate, is given by monthly injection. While this makes the need for injections less burdensome, side effects of therapy will persist for the duration of therapy. Thus, side effects from elagolix may be more rapidly reversed than with GnRH agonists.[23,31] While oral therapy may be more convenient, once or twice daily dosing of elagolix may lead to increased medical non-compliance. Moreover, in contrast to GnRH agonists, elagolix does not produce the "flare" or surge in hormones that leuprorelin acetate causes in the first few weeks of treatment. The flare can often lead to increased menstrual bleeding and other side effects that some women described as being uncomfortable.[22]

The effects of elagolix appear to be dose dependent. Whereas GnRH agonists work by fully suppressing hormone levels leading to amenorrhea in 75-98% of women, elagolix 150 mg led to amenorrhea in less than 31% of women.[24,31] High-dose elagolix (i.e., 200 mg BID), on the other hand, led to amenorrhea in 45-67% of women in the Phase III trials at six months.[24] In extension trials of an additional 6-months of therapy, amenorrhea was reported in 20-27% of those on 150 mg daily and 61-63% of those on 200 mg twice daily. The importance of this dose-dependent hormone suppression is unclear. It appears that the degree of symptomatic improvement is less with lower doses of elagolix, but side effects may also be lower, especially harmful bone mineral density reductions.

However, partial suppression of hormones may increase the likelihood of a woman becoming pregnant while taking elagolix. The safety of elagolix on a fetus is unknown and the use of non-hormonal contraception is required when using elagolix, especially at lower doses. Of the 23 pregnancies that occurred during EM-I and EM-II, 8 were in women taking elagolix (six in the 150

mg group and two in the 200 mg group). Of these 8 pregnancies, three resulted in live births without congenital anomalies; other pregnancies were terminated (n=2), lost to follow-up (n=2), or spontaneously aborted (n=1).[24] In Phase II studies, there were at least 4 pregnancies reported to be carried to term with one pregnancy resulting in a cleft palate and one resulting in a tracheal fistula.[34] As a result, the FDA is requiring post-approval studies to monitor pregnancies that occur during use of elagolix and to assess maternal and fetal outcomes.[68]

It is unclear how elagolix will affect racial, ethnic, gender, socio-economic, or regional disparities. If the cost of treatment is significant, those with limited financial resources may find it difficult to afford treatment. Lack of access to high quality endometrial care may also play a role in poor diagnosis and management overall. In general, patients and advocates highlighted the importance of a multidisciplinary care team and lack of research to identify the cause of endometriosis and the development and testing of new treatments. Though they expressed interest in new therapies for women with endometriosis, they did not view this as a game changing therapy. Indeed, some who feel that excisional surgery is underutilized expressed concern that elagolix may result in delaying surgery while this new medicine is tried. Thus, it is unclear if the introduction of elagolix will be viewed as addressing the disparities cited as leading to a perceived lack of attention by the medical community to this common, debilitating condition.

5.2 Contextual Considerations

Elagolix represents the first new treatment for endometriosis in over a decade. The arrival of any new treatment option is seen as a positive in a disease with no known cure. Funding for research in endometriosis has lagged other disease areas.[79,80] Manufacturers have recently begun to identify the large unmet medical need and propose new molecules to treat the six to ten million women thought to potentially suffer from the disease in the United States.[2,4,35,79]

Women with moderate-to-severe endometriosis-related pain may have not responded to first line therapies and thus evidence on elagolix and safety may not apply to women with milder disease, as they may be different than those included in the trials. Additionally, it is not clear whether all women with endometriosis receive an adequate trial of lower cost agents before discontinuing or switching to higher cost agents.

In our scoping calls, we heard that physicians hope that they can treat women with GnRH antagonists who respond well to treatment for long periods of time by adding hormone replacement therapy to protect against bone mineral loss. There is evidence that this is effective in GnRH agonist treatment; however, there are no published trials looking at add-back therapy with elagolix in endometriosis.[31] The Equinox Study of elagolix plus add-back therapy in women with endometriosis is underway (https://clinicaltrials.gov/ct2/show/NCT03213457?term=elagolix&cond=endometriosis&rank=2). Other ongoing studies of elagolix with add-back therapy in other conditions (i.e., uterine fibroids)

are closer to completion but have not yet been reported at a conference or in a peer-reviewed journal.[81] Due to a lack of information on add-back therapy, FDA prescribing information does not recommend using elagolix with estrogen containing contraceptives. As a result, therapy with high dose elagolix (200 mg twice a day) is limited to 6 months.

Patients and patient advocates we spoke with for this report expressed a concern that drug manufacturer's interests may influence guideline recommendations. There is a belief that industry interests have led to a focus on medical treatments and the result has been that surgical treatment is viewed in a more unfavorable light than they believe true. While patient advocates acknowledge that surgery may not be effective for many reasons, they provided strong testimony that excision surgery (as opposed to ablative surgery) performed by a surgical expert in endometriosis has been life altering for them.

Some patients suggested that low reimbursement for endometrial surgery may preclude many women from being offered more extensive excisional procedures that they view represent optimal surgical care in the US.[79,80] There was also concern that some OB/GYN doctors who perform surgery on women with endometriosis may not be adequately trained to perform more aggressive surgical procedures. In our review, we spoke to experts and advocates as well as found reports that describe investment in uterine fibroids taking precedence over investment in endometriosis.[35]

6. Value-Based Price Benchmarks

Value-based benchmark prices for elagolix, when compared to no active medical management, are presented in Table 6.1. As mentioned previously, the 200 mg twice-daily dose of elagolix is FDA-approved for a six-month treatment duration only; while the eventual duration of use of elagolix in typical practice remains unknown, we nevertheless present value-based benchmarks for both the short-run and long-run time horizons below to illustrate the range of discounts from WAC that may be required.

Table 6.1. Value-Based Benchmark Prices for Elagolix

	Annual WAC	Annual Price to Achieve $100,000 per QALY Threshold	Annual Price to Achieve $150,000 per QALY Threshold	Discount/ Price Premium 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%

*Represent 6 months duration, as seen in the trials
QALY: Quality-adjusted life year
All threshold prices rounded to the nearest $100
"+" indicates price premium

7. Potential Budget Impact

7.1 Overview

We used the cost-effectiveness model to estimate the potential total budgetary impact of elagolix in adult pre-menopausal women with moderate-to-severe endometriosis-associated pain. We used the placeholder price and the three threshold prices for elagolix in our estimates of budget impact.

7.2 Methods

We used results from the same model employed for the cost-effectiveness analyses to estimate total potential budget impact. Potential budget impact was defined as the total differential cost of using each new therapy rather than relevant existing therapy for the treated population, calculated as differential health care costs (including drug and non-drug costs) minus any offsets in these costs from averted health care events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time and to allow a more realistic impact on the number of patients treated with the new therapy.

The potential budget impact analysis included the candidate populations eligible for treatment: women in the United states between 18 and 49 years of age, diagnosed with moderate-to-severe endometriosis-related pain. Fuldeore and Soliman estimated the size of the prevalent diagnosed endometriosis population at 6.1% in women between 18 and 49 years, based on an online cross-sectional survey conducted in 2012. Although the elagolix trials included only patients with a surgical diagnosis for endometriosis, we are currently unsure if elagolix will be used to treat patients with non-surgically diagnosed endometriosis. We hence did not include this filter when estimating the eligible population for elagolix. However, we excluded those who had undergone a hysterectomy (29.2%). Applying this criterion resulted in a prevalence estimate of approximately three million women with diagnosed endometriosis without hysterectomy. We found no published literature on the percentage of women with moderate-to-severe endometriosis-related pain, and hence relied on estimates on severity of symptoms as reported by Fuldeore and Soliman. We assumed that women with "extremely bothersome" symptoms of dysmenorrhea and/or nonmenstrual pelvic pain represented those with moderate-to-severe endometriosis-related pain. Since percentages in this category were not cumulative in Fuldeore's and Soliman's analysis, we assumed the higher of the two percentages, namely, percentage with "extremely bothersome" dysmenorrhea (44.3%) as those with moderate-to-severe endometriosis.[2] Applying this estimate to the U.S. 2018 estimated to 2022 projected population resulted in approximately 1.3 million patients representing the target population prevalence, or approximately 270,000 patients each year over five years.[40]

ICER's methods for estimating potential budget impact are described in detail elsewhere and have recently been updated. The intent of our revised approach to budgetary impact is to document the percentage of patients that could be treated at selected prices without crossing a budget impact threshold that is aligned with overall growth in the US economy.

Briefly, we evaluate a new drug that would take market share from one or more drugs and calculate the blended budget impact associated with displacing use of existing therapies with the new intervention. In this analysis, we assumed that elagolix 200 mg twice daily would replace no active treatment, which primarily included rescue analgesics used to treat endometriosis-associated pain.

Using this approach to estimate potential budget impact, we then compared our estimates to an updated budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA over the most recent two-year period, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 7.1.

For 2017-18, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage access and affordability is calculated to total approximately $915 million per year for new drugs.

Table 7.1. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2017 (est.) +1%	3.20%	World Bank, 2016
2	Total health care spending, 2016 ($)	$2.71 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	17.7%	CMS National Health Expenditures (NHE), 2016; Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$479 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.3 billion	Calculation
6	Average annual number of new molecular entity approvals, 2015-2016	33.5	FDA, 2017
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$457.5 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$915 million	Calculation

7.3 Results

Table 7.2 illustrates the per-patient budget impact calculations in more detail, based on elagolix's WAC ($10,138 per year), assumed net price ($7,400 per year) and the prices to reach $150,000 ($12,800 per year), $100,000 ($8,800 per year), and $50,000 ($4,700 per year) per QALY compared to no active treatment.

The average potential budgetary impact when using the WAC and assumed net price was an additional per-patient cost of approximately $6,800 and $4,800 annually, respectively. Average potential budgetary impact at the three cost-effectiveness threshold prices ranged from approximately $8,800 per patient at the price to achieve $150,000 per QALY to approximately $3,000 at the price to achieve a $50,000 per QALY cost-effectiveness threshold (Table 7.2). The total population budget impact annually at elagolix's WAC and assumed net price were approximately $5.2 billion and $3.7 billion.

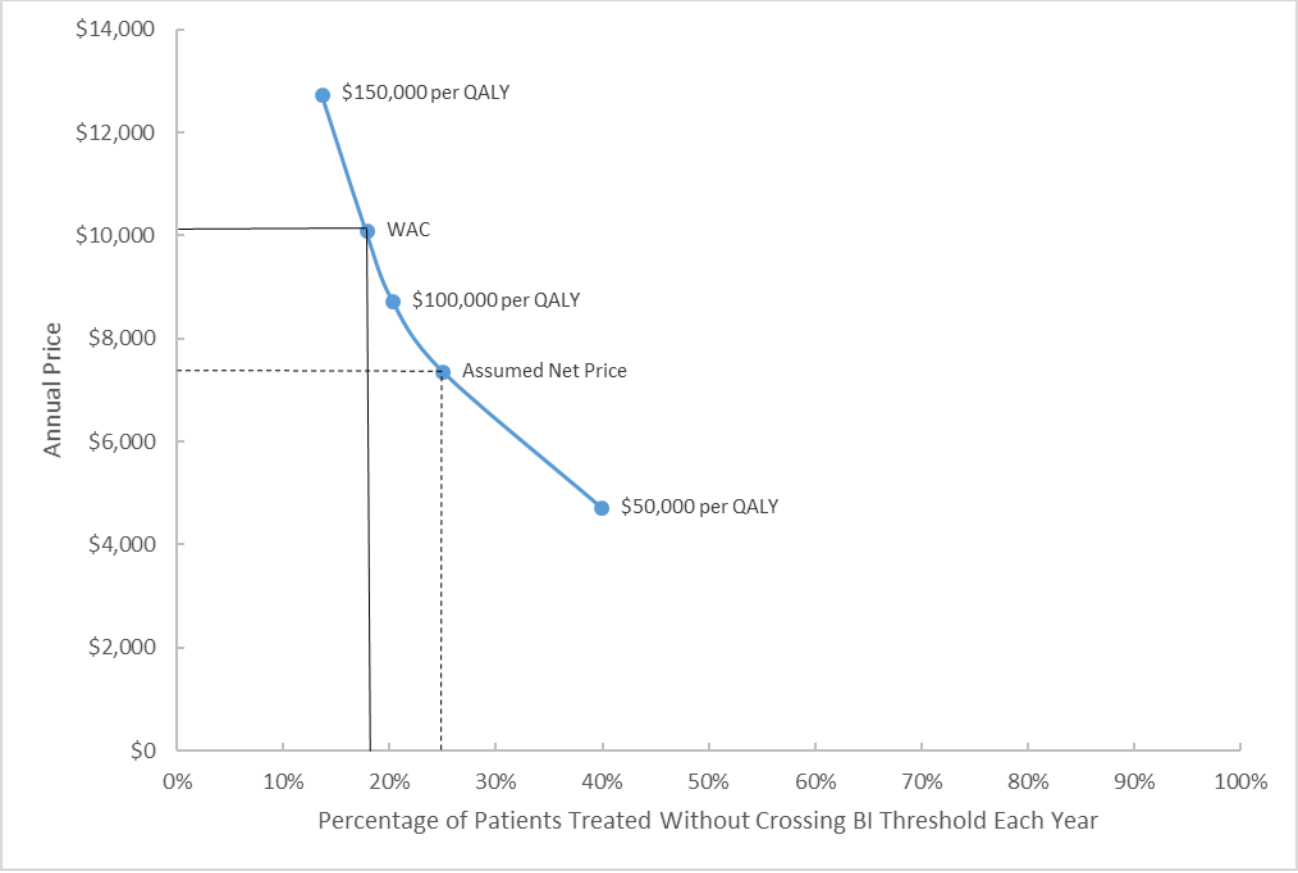
Table 7.2. Per-Patient Budget Impact Calculations Over a Five-Year Time Horizon when Treating Moderate-to-Severe Endometriosis-Related Pain

	Average Annual Per Patient Budget Impact				
	WAC	Assumed Net Price	$150,000/QALY	$100,000/QALY	$50,000/QALY
Elagolix 200 mg Twice Daily	$8,542	$6,605	$10,620	$7,711	$4,801
No Active Treatment	$1,789				
Difference	$6,753	$4,817	$8,832	$5,922	$3,013

WAC: Wholesale Acquisition Cost
QALY: Quality-Adjusted Life Year

As shown in Figure 7.1, only 18% of eligible patients could be treated in a given year without crossing the ICER budget impact threshold of $915 million at elagolix's WAC, while 25% of patients could be treated without crossing this same threshold at elagolix's assumed net price. Between 13% and 40% of patients could be treated in a given year without crossing the budget impact threshold at the $150,000 per QALY to $50,000 per QALY threshold price range.

Figure 7.1. Potential Budget Impact Scenarios at Different Prices of Elagolix to Treat Adult Premenopausal Women Diagnosed with Moderate-To-Severe Endometriosis-Related Pain



In summary, the annual budget impact of elagolix (using the assumed net price) in the eligible endometriosis population, relative to no active treatment resulted in approximately an additional $4,800 per patient in costs per patient to the health system. The total budget impact exceeded the ICER annual budget impact threshold of $915 million at all prices of elagolix relative to no active treatment. At its assumed net price, only a quarter of the eligible population could be treated annually with elagolix before reaching an annual budget impact threshold linked to overall US economic growth.

7.4 Access and Affordability

At the July 12th public meeting, there was general agreement that, despite the availability of alternative treatments for the medical management of moderate-to-severe endometriosis pain, the potential patient population that can be treated with elagolix remains large. Additionally, since elagolix is an oral agent, patients and clinicians may prefer it over other treatments such as GnRH agonists. There can be a rapid return of endometriosis symptoms once elagolix has been discontinued; therefore, if benefit is seen early on in treatment with elagolix, patients and clinicians may wish to use this drug long-term, thus leading to higher treatment costs.

Our estimates of potential budget impact of elagolix indicated that at its net price, assuming a 27% discount from WAC, only 25% of all eligible patients could be treated before costs exceeded ICER's potential budget impact threshold of $915 million per year. Given that optimal clinical uptake at current estimated discount prices would lead to 5-year costs far in excess of this threshold, ICER is issuing an Access and Affordability Alert at this time. 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.

8. Summary of the Votes and Considerations for Policy

8.1 About the NE CEPAC Process

During New England CEPAC public meetings, the CEPAC panel deliberates and votes on key questions related to the systematic review of the clinical evidence, economic analysis of the applications of treatments under examination, and the supplementary information presented. Panel members are not pre-selected based on the topic being addressed and are intentionally selected to represent a range of expertise and diverse perspectives.

Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, subject matter experts are recruited for each meeting topic and provide input to NE CEPAC panel members before the meeting to help clarify their understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the NE CEPAC panel during their deliberation, and help to shape recommendations on ways the evidence can apply to policy and practice.

After the NE CEPAC Panel votes, a policy roundtable discussion is held with the NE CEPAC panel, clinical experts, patient advocates, payers, and when feasible, manufacturers. The goal of this discussion is to bring stakeholders together to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on policy roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the July 12, 2018 meeting, the New England CEPAC panel discussed issues regarding the application of the available evidence to help patients, clinicians, and payers address important questions related to the use of elagolix for treating patients with endometriosis. Following the evidence presentation and public comments (public comments from the meeting can be accessed here, starting at minute 01:20:30), the NE CEPAC panel voted on key questions concerning the comparative clinical effectiveness, comparative value, and potential other benefits and contextual considerations related to elagolix. These questions are developed by the ICER research team for each assessment to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice, medical policy decisions, and patient decision-making. The voting results are presented below, along with specific considerations mentioned by the CEPAC panel members during the voting process.

During this meeting, the NE CEPAC panel did not deliberate or vote on the value of elagolix because the manufacturer had not yet announced the launch price, and ICER's economic evaluation had

therefore used a placeholder price. Furthermore, the majority of the NE CEPAC panel voted that the evidence was not adequate to determine that elagolix provided a net health benefit compared to no treatment, thus rendering a vote on value unnecessary. The full discussion and vote tallies are summarized below.

8.2 Voting Results

1) Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by no treatment?

Yes: 1 votes	No: 11 votes

Comments: The majority of the panel voted that there was not adequate evidence to demonstrate that elagolix offered a positive net health benefit compared to no treatment. Those who voted no argued primarily that there was a lack of long-term data on the benefits and safety of a medicine that may be used for a chronic condition on a long-term basis. This included whether there could be long-term risk, such as bone loss and cardiovascular risk, even after discontinuing short-term use of elagolix. At the time of the CEPAC meeting there were also additional concerns about safety based on the FDA decision in March to postpone a decision on elagolix due to the need to review liver function test results. The rationale for this delay was never stated publicly, nor did the manufacturer respond to requests to share details with ICER prior to the CEPAC meeting. It is not possible to know how the votes of the CEPAC would have changed had the meeting been held after FDA approval, when no mention of liver safety issues was included in the labeling information. Only one panelist at the meeting voted that the evidence was adequate to support elagolix based on available short-term efficacy and safety data, as well as the argument that providing patients and their clinicians this medicine would provide additional treatment options beyond those currently available.

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?

Yes: 0 votes	No: 12 votes

Comment: All panelists voted that the evidence was not sufficient to distinguish the health benefits and risks of elagolix and the GnRH agonist leuprorelin acetate. This was based upon limited available data comparing these agents in a single, small Phase II trial that had a number of important limitations and also showed no material differences in key outcomes. Panelists felt that the FDA could require future studies to assess the comparative outcomes of these drugs, particularly with higher-dose elagolix (200 mg twice daily).

3) Is the evidence adequate to demonstrate that the net health benefit of elagolix is superior to that provided by hormonal contraceptive, depot medroxyprogesterone?

Yes: 0 votes	No: 12 votes

Comment: All panelists voted that the evidence was not sufficient to distinguish the health benefits and risks of elagolix and the hormonal contraceptive depot medroxyprogesterone acetate. As above, this was based upon the limited available data comparing these agents in a single, small Phase II trial that had a number of important limitations and also showed no material differences in key outcomes. Panelists felt that future studies should compare the use of hormonal contraceptives and lower dose elagolix (150mg daily) in patients with less severe symptoms due to endometriosis.

4) When compared to no treatment, does elagolix offer one or more of the following "potential other benefits"? (select all that apply)

# of Votes	Other Benefits
0/12	This intervention offers reduced complexity that will significantly improve patient outcomes.
4/12	This intervention will reduce important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.
4/12	This intervention will significantly reduce caregiver or broader family burden.
9/12	This intervention offers a novel mechanism of action or approach that will allow successful treatment of many patients who have failed other available treatments.
5/12	This intervention will have a significant impact on improving patient's ability to return to work and/or their overall productivity.
6/12	Other important benefits.

Comment: No voting members of the CEPAC panel thought that elagolix would reduce the complexity of care in a way that would significantly improve patient outcomes. This was based upon the treatment offering short-term benefits for a chronic condition and uncertainty around whether elagolix could be used as a long-term therapy. Studies demonstrated that symptoms return after discontinuing elagolix and patients will continue to be faced with complex treatment decisions involving tradeoffs between benefits and harms, as well as when surgical interventions are indicated.

Few panelists felt there was evidence that elagolix would reduce important health disparities. Panelists highlighted comments from patients and patient advocates about the lack of research funding for women's health issues. Though elagolix may offer

another option for women with endometriosis who haven't responded to first line therapies, it was not felt to be the breakthrough therapy that patients and panelists felt is needed to result in a meaningful decrease in gender health disparities. In addition, the published studies of elagolix included few non-white patients and did not provide information on socioeconomic characteristics of patients.

Regarding caregiver burden, CEPAC panelists pointed to the lack of good data on the impact of elagolix on caregiver or broader family burden. Similarly, while there were no data reported on work or productivity outcomes, decreased pain symptoms and improved functional outcomes associated with elagolix may improve outcomes. To have a meaningful impact on work and productivity, elagolix will need to be given for prolonged periods or as part of a treatment plan that can control symptoms with acceptable side effects over longer periods of time.

Most panelists allowed that elagolix provided an important and somewhat novel approach to treating patients with endometriosis, especially for those who have not responded to other available treatments or have had side effects that limit their use. Panelists also heard from specialists who said that elagolix could also be considered for patients who initially benefited from surgery but had a recurrence of symptoms over time.

5) Are any of the following contextual consideration important in assessing long-term value for money? (select all that apply)

# of Votes	Contextual Considerations
10/12	This intervention is intended for the care of individuals with a condition of particularly high severity in terms of impact on length of life and/or quality of life.
8/12	This intervention is intended for the care of individuals with a condition that represents a particularly high lifetime burden of illness.
1/12	This intervention is the first to offer any improvement for patients with this condition.
9/12	Compared to no treatment, there is significant uncertainty about longterm risk of serious side effects.
9/12	Compared to no treatment, there is significant uncertainty about the magnitude or durability of long-term benefits.
7/12	Other important contextual considerations

Comment: A majority of panelists voted affirmatively that elagolix is intended for patients with a condition of particularly high severity in terms of impact on quality of life; similarly, elagolix is intended for the care of individuals with a high symptomatic burden that has not responded to prior treatments.

Panelists generally disagreed that elagolix represented the first intervention to offer improvement for patients with endometriosis based upon the prior availability of FDA and non-FDA approved treatments for endometriosis, including medical and surgical therapies.

Most panelists were concerned about the uncertainty around the long term benefits and risks of elagolix, including whether bone loss and cholesterol changes returned to baseline after stopping therapy. There was also uncertainty about the durability of long term benefits of using elagolix over a prolonged time period.

6) Given the available evidence on comparative clinical effectiveness and the incremental cost effectiveness, and considering other benefits and contextual considerations, what is the longterm value for money of elagolix compared with no active treatment?

Low: N/A	Intermediate: N/A	High: N/A

Comment: The panel did not vote on elagolix's value in comparison to no treatment for two reasons: (1) at the time of the meeting, the launch price for elagolix was not yet know and ICER therefore used a placeholder price in its economic analysis; (2) the panel voted that the evidence was not adequate to determine a net health benefit in comparison to no treatment.

8.3 Roundtable Discussion and Key Policy Implications

Following its deliberation on the evidence, the New England CEPAC Panel engaged in a moderated discussion with a policy roundtable about how best to apply the evidence on elagolix in treating patients with endometriosis to policy and practice. The policy roundtable members included two patient representatives; two clinical experts, representing the fields of obstetrics and gynecology; and two payers, both public and private. The drug manufacturer of elagolix was invited to send representatives to the meeting, but declined this invitation. 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. The names of the Policy Roundtable participants are shown below, and conflict of interest disclosures for all meeting participants can be found in Appendix H.

Table 8.1 Policy Roundtable Members

Name	Title and Affiliation
Casey Berna, MSW	Endometriosis and Infertility Patient Advocate
William Brewster, MD, FACP, CHIE	Vice President; Harvard Pilgrim Health Care, New Hampshire Market
Rebecca Flyckt, MD	Director, Fertility Preservation Program, Obstetrics, Gynecology and Women's Health Institute; Cleveland Clinic
Heather Guidone, BCPA	Patient Advocate; Program Director, Center for Endometriosis Care; Executive Board Member; Endometriosis Research Center
Nancy Hogue, PharmD	Director of Pharmacy Services; Department of Vermont Health Access
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

The roundtable discussion was facilitated by Dr. Dan Ollendorf, PhD, Chief Scientific Officer of ICER. The main themes and recommendations from the discussion are organized by audience and summarized below.

Payers

(1) Elagolix has known short-term side effects and no long-term comparative safety and efficacy data in relation to several other well-established treatment options for endometriosis. It is therefore reasonable for insurers to develop prior authorization criteria for elagolix to ensure prudent use.

Elagolix, a GnRH antagonist, has a new mechanism of action with known short-term side effects and lacks comparative long-term safety and efficacy data in relation to oral contraceptives or to GnRH agonists that are current options for second-line pharmaceutical therapy. It is therefore reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of elagolix.

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 are discussed below.

Potential patient eligibility criteria:

a. **Premenopausal women with symptomatic endometriosis who have had inadequate symptom relief after at least three months of first-line therapy with nonsteroidal anti-inflammatory meds (NSAIDs) and hormonal contraceptives.**

Guideline recommendations highlight that first-line therapy for women with symptomatic endometriosis includes NSAIDs and hormonal contraceptives. If adequate improvement in symptoms is not seen after a trial of these medicines, then consideration of second-line therapies or possibly surgical intervention would be appropriate. Experts during the roundtable discussion highlighted that a 3-6 month trial represented an amount of time in which a response would be expected to first-line therapy. This would also encompass a minimum duration of disease, suggested to be at least six months of symptoms attributed to endometriosis by clinical experts.

b. The lack of comparative data favoring the safety or effectiveness of elagolix over leuprorelin acetate suggests that insurers may explore the option of requiring a trial of leuprorelin acetate prior to coverage for elagolix. For insurers contemplating this step therapy coverage approach, several important factors should be considered.

As a GnRH agonist, leuprorelin acetate (Lupron Depot®; AbbVie) is an approved second-line treatment affecting the same hormonal pathway as elagolix, though by a different mechanism. Leuprorelin acetate may soon be available in generic formulations, raising the possibility that its price will become much lower than that for elagolix. Since there is inadequate evidence with which to compare the relative effectiveness of leuprorelin acetate and elagolix, insurers may explore the option of covering elagolix only after a trial of less-expensive leuprorelin acetate, extending the existing step-therapy protocols that frequently mandate initial use of oral contraceptives and NSAIDs before second-line therapy is considered. If they do explore this option, insurers should carefully consider clinical expert and patient input regarding the importance of those elements that distinguish elagolix from leuprorelin acetate, including the time needed for reversibility of side effects, the mode of administration, and the duration of action.

Potential provider criteria:

c. Elagolix may be covered only if prescribed by a specialist clinician with formal training in obstetrics/gynecology or reproductive endocrinology.

Assessing patients with symptomatic endometriosis for whom first-line therapies have not provided adequate response requires management by a clinician with expertise in this clinical area. Clinical experts and patient advocates at the CEPAC meeting suggested that women with moderate to severe symptoms of endometriosis should usually be referred to clinicians with specialized training and experience. However, it was acknowledged that in some regions, subspecialists with this level of training may not be available, and that many women with endometriosis are successfully cared for by generalist obstetrician-gynecologists, family practitioners, and general internists. Insurers may therefore consider

limiting provider prescribing of elagolix to subspecialists but should consider the potential impact on access for some patients. One option may be to require generalist prescribers of elagolix to seek consultation from subspecialists through telehealth or other methods.

Potential limitations on initial length of coverage:

d. 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. Insurers may require that coverage beyond that time requires clinician attestation of clinical improvement and documentation that lipids and bone mineral density are being monitored.

Coverage for new expensive therapies like elagolix is frequently limited in duration at the outset in order to assure that clinicians and patients discuss the initial outcomes of treatment and affirm that the clinical benefit gained is worth the side effects of continuing treatment. Phase III trials for elagolix assessed six-months duration of therapy, and FDA approval of elagolix is limited to six-months at the higher dose and for a maximum of two years at the lower dose. Under these circumstances, and with clinical experience with leuprorelin acetate suggesting that many patients may continue with chronic treatment for extended time periods, limiting initial coverage of elagolix to a six-month period would not be an unreasonable consideration. Even for the lower dose of elagolix, there is no evidence showing the benefits or harms of use beyond six months in any published trials and no comparative studies with other therapies such as hormonal contraceptives.

Insurers may wish to consider linking approval for continued coverage beyond six months with demonstration that clinicians are adequately documenting and monitoring potential side effects, specifically adverse increases in lipids and a decrease in bone mineral density. Requiring documentation testing for these side effects should not create an undue burden on clinicians or patients and may serve as an important safeguard.

Manufacturers

(2) 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.

Those attending the roundtable noted the absence of the manufacturer, the stakeholder who will continue to play a central role in bringing elagolix into clinical practice, collaborating with patients and clinicians in future research, and negotiate with insurers over coverage and payment terms. Discussants encouraged this manufacturer, and other

manufacturers more generally, to be willing to engage in an independent process like the NE CEPAC deliberations to share perspectives on how best to apply evidence to these clinical and policy questions, and to evaluate fair pricing of new therapeutics based on the added clinical benefit to affected patients. This process should fully engage a broad range of relevant participants including the innovator of the new therapeutic, as well as patients, patient advocacy groups, clinical experts, insurers, and other stakeholders. Patient advocates voiced the need for efforts, such as these, to improve the trust that they felt was missing between patients, clinicians, and manufacturers in the process of studying elagolix and bringing this potentially important medication to women suffering the effects of inadequately treated endometriosis.

(3) 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.

The published trials of elagolix do not provide enough information for clinicians or patients to be able to understand the impact of disease stage or prior treatment use on patient outcomes, making it impossible to judge which patients are most likely to benefit from treatment. Clinical trials have eligibility criteria, treatment restrictions during the study period, and use of primary outcomes that may make it difficult for patients and clinicians to understand how the study drug may end up working when introduced into clinical practice. Vaguely-defined eligibility criteria may mean that patients in the clinical trials differ from patients who may be most likely to be treated with the drug in usual practice. The inclusion and exclusion criteria used in the Phase III trials of elagolix led to a heterogenous study population that may not reflect the average patient who may use this drug when introduced into clinical practice. Patients may not have been tried on certain therapies commonly used to treat endometriosis prior to study enrollment.

Though the study results demonstrated positive outcomes, available data make it difficult to identify who may derive the greatest net benefit; for example, elements like disease stage were notably missing from reported baseline characteristics, and candidate patients had previously responded to (rather than failed) prior treatments.

(4) Manufacturers and researchers in the area of endometriosis owe patients, clinicians, and insurers better information on the long-term comparative clinical effectiveness and value of innovative new therapies. For elagolix, they should take action to ensure that future studies are developed to directly compare elagolix with other treatment options using standardized research protocols that focus on outcomes that reflect what matters most to patients.

For symptomatic patients with endometriosis, the CEPAC panel voted that there was inadequate evidence to distinguish the net health benefit between elagolix and other treatment options including GnRH agonists and hormonal contraceptives. The GnRH agonist leuprorelin acetate, and the hormonal contraceptive depot medroxyprogesterone were directly compared to elagolix in Phase II trials that were limited by small sample sizes, incomplete reporting and imbalances in baseline characteristics, differential measurement of key outcomes, short duration of follow-up, high attrition, and limited statistical testing. No studies have directly compared elagolix and aromatase inhibitors.

The Phase III studies used primary outcomes that reported pain separately for dysmenorrhea and nonmenstrual pelvic pain. However, patients and clinicians want to know what the overall pain response will be and whether the net benefit may remain positive over time, especially compared to other medical and surgical treatment options. To address the need for a single measure of clinical benefit, the ICER cost effectiveness modeling used a derived outcome that sought to combine separate primary outcomes into a combined net response. In general, manufacturers, researchers, and regulators should collaboratively develop standard approaches for trial recruitment, entry criteria, study duration, and measurement of key outcomes to facilitate comparisons across trials.

Roundtable participants highlighted the need for comparative trials, especially studies 1) comparing high dose elagolix (200mg twice daily) versus leuprorelin acetate for patients with moderate-to-severe symptoms of endometriosis who have failed first line therapies, and 2) low dose elagolix (150mg daily) versus low dose hormonal contraceptives for patients with less severe symptoms of endometriosis, or who have had laparoscopic surgery and develop recurrent symptoms. Of note, post-marketing FDA requirements for elagolix focused on pregnancy-related outcomes and the co-administration of elagolix with combined oral contraceptives, but not comparative studies of established therapies.

Patient Advocacy Organizations and Professional Societies

(5) 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.

During the policy roundtable discussion, patient advocates and clinical experts highlighted the lack of basic research into the underlying mechanisms resulting in endometriosis. Patient advocacy organizations and professional societies can help funding agencies, such as NIH and PCORI, to prioritize available resources to support women's health issues that affect a large number of individuals and have a major impact on health and well-being. There is ample evidence that endometriosis is such a condition. Roundtable participants also highlighted the need for research on new therapeutic targets based upon a basic understanding of the disease mechanism. Similarly, for manufacturers, there is a need to increase clinical trials of therapies targeting women's health conditions such as endometriosis. Patient advocates pointed to the fact that elagolix represents the first new FDA-approved therapy for endometriosis in over 20 years. And yet, patient enthusiasm for elagolix as discussed during the roundtable is limited because it is viewed as working in a similar way to GnRH agonists, demonstrating modest benefits but side effects that are difficult for women to tolerate. There was also concern that elagolix doesn't represent a long-term treatment option because of the long-term risks that appear to be similar to that of GnRH agonists.

(6) Professional societies should take steps to address and minimize potential financial and professional conflicts of interest; and to collaborate with patients and methodological experts in new efforts to develop comprehensive and unbiased guidelines and educational outreach for patients with endometriosis.

Roundtable participants discussed a number of important concerns that may undermine the trust among patients with endometriosis and clinicians caring for them. Patient advocates stated that there was a need to improve trust among key stakeholders and one way to do this was for professional societies to include the patient voice when developing practice guidelines. A key impediment to trusting guideline recommendations raised by patient advocates was the appearance of conflicts of interest in the guideline development process. Support received by professional societies and patient advocacy organizations from industry sponsors who have or may be developing therapeutics that are part of the guideline recommendations was felt to be an important source of conflict of interest. Increasing trust goes beyond just reporting these contributions; there need to be efforts to directly minimize the potential appearance of conflict or influenced judgment that such support causes.

Additionally, ensuring guideline participants included a wide range of stakeholders was viewed as helping to lead to trust with the published recommendations. Stakeholders should include patients with the condition, clinicians from all relevant specialties treating such patients as well as generalists, and experts in summarizing data from research studies and guideline development. Not only should efforts be made to ensure that guidelines are developed using rigorous methods, there is the need to provide explicit disclosure and monitoring of potential conflicts of interest.

It was also thought important for relevant professional societies to develop and update clinical practice guidelines, especially when new therapeutic options become available. Placing these new agents into practice and helping clinicians identify their role in a changing landscape is critical to ensuring clinicians have the knowledge to wisely use the new therapies.

Finally, obstetrics-gynecology and endocrine professional societies should work together in such guideline efforts, and include recommendations on interdisciplinary management. The concept of centers of excellence within regions of the U.S., where clinicians with challenging cases can refer patients, was mentioned as one way to better organize care. Professional societies could help determine how they should be developed, the criteria for eligibility and ongoing certification, and interdisciplinary services available, including alternative therapies, mind-body techniques and diet/nutrition instruction.

Regulators

(7) Regulators have an important role to play in how new therapeutics enter clinical practice and therefore 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.

The patient population which may be considered for treatment with elagolix is very large. It is unlikely that the manufacturer will feel it has financial incentives to invest in further studies to define long-term risks and benefits, or to evaluate subpopulations which may have distinctive risks or benefits. The FDA's consideration of elagolix for use in patients with endometriosis was based upon short-term outcomes of randomized controlled trials (up to six months). As might be expected from its short half-life, studies show a rapid return of symptoms with cessation of elagolix. Therefore, if initial benefit is found, patients and clinicians may wish to use this drug on a long-term basis.

During the roundtable discussion, clinical experts described how patient with evidence of benefit from short-term elagolix therapy may be transitioned to other treatments, such as

hormonal contraceptives. But they acknowledged that if symptoms recurred, resuming elagolix would be a reasonable option. Though the manufacturer has performed and reported single arm, long-term follow-up on elagolix without active comparators, it is uncertain what the long-term relative benefits of elagolix will be compared to other treatments. Therefore, regulators should require manufacturers to perform long-term comparative outcome studies within a well-defined period of time after drug approval to provide patients, clinicians and payers with evidence to support ongoing use and coverage for this drug.

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This is the first NE CEPAC review of elagolix in treating endometriosis.

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APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist Item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table A2. Search Strategies for Clinical Studies of Elagolix

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R) 1946 to Present and Cochrane Central Register of Controlled Trials

1	exp endometriosis/
2	(adenomyo$ or endometriosis$).tw.
3	(adenomyo$ or endometrio$).tw.
4	chocolate cyst$.tw.
5	or/1-4
6	contraceptives, oral/
7	contraceptives, oral, synthetic/
8	contraceptives, oral, combined/
9	(combin$ adj3 (oral$ or hormon$) adj3 (pill$ or contracept$)).tw.
10	contraceptives, oral, hormonal/
11	contraceptive ring/
12	contraceptive ring.tw.
13	vaginal ring/
14	vaginal ring.tw.
15	contraceptive patch/
16	contraceptive patch$.tw.
17	progesterone/
18	progesterone congeners/
19	progesterone$.tw.
20	progestins/
21	(progestin$ or progestogen$ or gestagen$).tw.
22	dydrogesterone/
23	dydrogesterone$.tw.
24	norethindrone/
25	(norethindrone$ or norethisterone$).tw.
26	levonorgestrel/
27	levonorgestrel$.tw.
28	medroxyprogesterone 17-acetate/
29	medroxyprogesterone$.tw.
30	depo.tw.
31	dmpa.tw.
32	dienogest/
33	dienogest.tw.
34	intrauterine devices, medicated/
35	lng-ius.tw.
36	mirena.tw.

37	((intrauterine$ or intra uterine$) adj3 levonorgestrel$).tw.
38	gonadotropins/
39	gonadotrop?in$.tw.
40	GnRH$.tw.
41	GnRH/
42	goserelin/
43	goserelin$.tw.
44	leuprolide/
45	(leuprolide$ or leuprorelin$).tw.
46	nafarelin/
47	nafarelin$.tw.
48	elagolix/
49	elagolix.tw.
50	degarelix/
51	degarelix.tw.
52	aromatase inhibitors/
53	aromatase inhibitor$.tw.
54	aromatase inhibit$.tw.
55	anastrozole/
56	anastrozole.tw.
57	letrozole/
58	letrozole.tw.
59	exemestane/
60	exemestane.tw.
61	or/6-60
62	5 and 61
63	(abstract or addresses or autobiography or bibliography or biography or clinical trial, phase i or case report or comment or congresses or consensus development conference or duplicate publication or editorial or guideline or in vitro or interview or lecture or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or personal narratives or portraits or practice guideline or review or video-audio media).pt.
64	cohort studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ or comparative study.pt.
65	control groups/ or (control* adj2 (clinical or group* or trial* or study or studies or design* or arm*)).ti,ab. or ("clinical trial" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or (random?ed adj6 (study or trial* or (clinical adj2 trial*))).ti,ab. or ((single or doubl*) adj2 blind*).ti,ab.
66	64 or 65
67	62 not 63
68	66 and 67
69	(animals not (humans and animals)).sh.
70	68 not 69
71	limit 70 to english language
72	remove duplicates from 71

* Run February 14, 2018

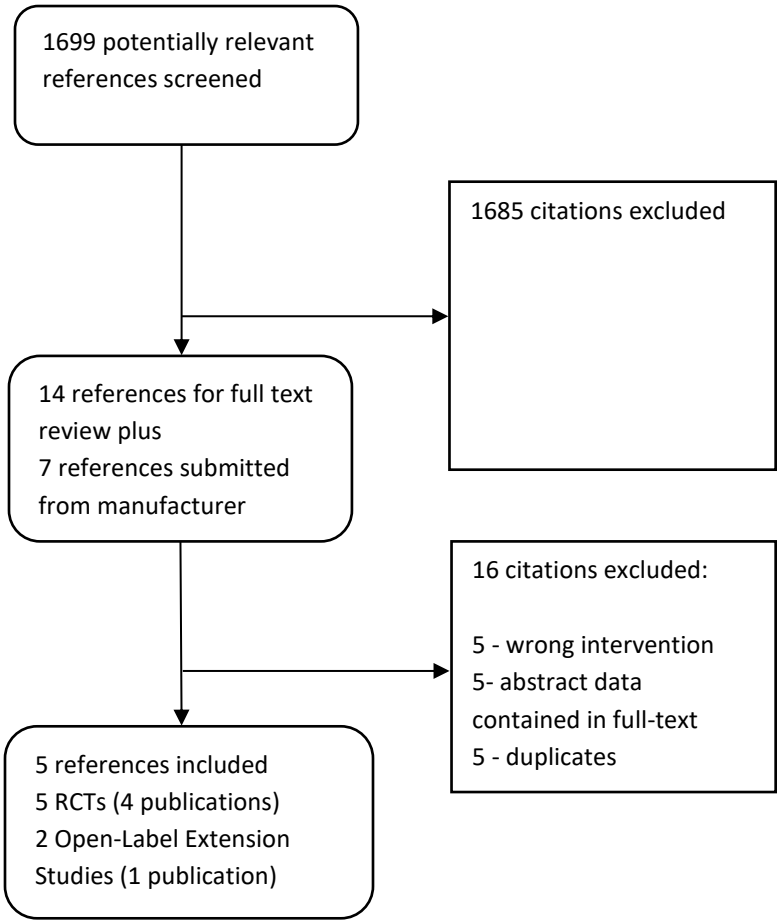
EMBASE search strategy

#1	'endometriosis'/exp OR 'endometriosis'
#2	'adenomyosis'/exp
#3	'chocolate cyst'
#4	#1 OR #2 OR #3
#5	'oral contraceptive agent'
#6	'vagina ring'
#7	'contraceptive ring'
#8	'contraceptive patch'
#9	'progesterone'
#10	'progesterone derivative'
#11	'dydrogesterone'
#12	'norethisterone'
#13	'levonorgestrel'
#14	'medroxyprogesterone acetate'
#15	'medroxyprogesterone'
#16	depo
#17	dmpa:de
#18	depo:de
#19	'dienogest'
#20	'intrauterine contraceptive device'
#21	'levonorgestrel releasing intrauterine system'
#22	mirena:ti,ab
#23	'gonadotropin'
#24	gnrh:de
#25	'gonadorelin'
#26	'gonadorelin agonist'
#27	'goserelin'
#28	'leuprorelin'
#29	'nafarelin'
#30	'elagolix'
#31	'degarelix'
#32	'gonadorelin antagonist'
#33	'aromatase inhibitor'
#34	'anastrozole'
#35	'letrozole'
#36	'exemestane'
#37	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
#38	#4 AND #37
#39	'animal'/exp OR 'nonhuman'/exp OR 'animal experiment'/exp
#40	'human'/exp
#41	#39 AND #40
#42	#39 NOT #41
#43	#38 NOT #42
#44	#43 NOT [english]/lim
#45	#44 AND [medline]/lim

#46	#45 AND ('chapter'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'review'/it OR 'short survey'/it)
#47	#45 NOT #46

* Run February 16, 2018

Figure A1. PRISMA Flow Chart Showing Results of Literature Search for Elagolix for Endometriosis-Related Pain



Appendix B. Coverage Policies

Table B1. Coverage Policies of Major Commercial Payers in New England

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont	
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighborhood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT	MVP Grp
Leuprorelin acetate (Trademark: Lupron; Manufacturer: AbbVie)													
Tier	NF	4	NF	MD	2	1	2	NF	MD	NF	1	2	MD
PA	Y	N	Y	Y	N	Y	N	Y	Y	NF	Y	N	Y
Diagnosis or pre-treatment by a specialist	Y	N	Y	Y	N	no info	N	Y	Y	NF	no info	N	N/A
Duration limitations (# of months)	12	N	12	12	no info	6	1	12	12	NF	6	N	N/A
Specialty	Y	N	Y	Y	Y	Y	N	Y	Y	NF	Y		Y
Goserelin (Trademark: Zoladex; Manufacturer: TerSera Therapeutics)													
Tier	NF	4	NF	NF	2	1	NF	NF	NF	4	1	2	MD
PA	Y	Y	Y	NF	N	Y	NF	Y	NF	N	Y	N	MD
Diagnosis or pre-treatment by a specialist	Y	no info	Y	NF	N	no info	NF	Y	NF	N	no info	N	MD
Duration limitations (# of months)	6	no info	Y	NF	no info	6	NF	6	NF	Y	6	N	MD

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont	
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighbor-hood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT	MVP Grp
Specialty	Y	Y	Y	NF	Y	Y	NF	Y	NF	Y	Y	N	MD
Nafarelin (Trademark: Synarel; Manufacturer: Pfizer)													
Tier	4	2	4	3	NF	3	2	4	3	2	3	NF	3
PA	Y	Y	Y	N	NF	N	N	Y	N	N	N	Y	N
Diagnosis or pre-treatment by a specialist	Y	no info	Y	N	NF	N	N	Y	N	N	N	NF	no info
Duration limitations (# of months)	6	no info	6	1	NF	N	1	6	1	N	N	NF	no info
Specialty	Y	no info	Y	N	NF	N	N	Y	N	N	N	NF	N
Aromatase Inhibitors													
Letrozole (Trademark: Femara; Manufacturer: Novartis)													
Tier	1	1	2	NF	1	1	1	2	NF	1	1	NF	1
PA	N	N	N	NF	N	N	N	N	NF	N	N	NF	N
Diagnosis or pre-treatment by a specialist	N	N	N	NF	N	N	N	N	NF	N	N	NF	N
Duration limitations (# of months)	N	N	N	NF	N	N	N	N	NF	N	N	NF	N
Specialty	N	N	N	NF	N	N	N	N	NF	N	N	NF	N
Exemestane (Trademark: Aromasin; Manufacturer: Pfizer)													

	Connecticut		Maine		Massachusetts			New Hampshire		Rhode Island		Vermont	
	Anthem (Wellpoint Inc Group)	Connecticare	Anthem (Wellpoint Inc Group)	HPHC Maine	BCBS of MA	Neighbor-hood Health Plan	Tufts Health Plan	Anthem (Wellpoint Inc Group)	HPHC New Hampshire	BCBS of RI	Neighborhood Health Plan of RI	BCBS of VT	MVP Grp
Tier	1	1	2	2	1	1	1	2	2	1	1	NF	1
PA	Y	N	Y	N	N	N	N	Y	N	N	N	NF	N
Diagnosis or pre-treatment by a specialist	NF for endo	N	NF for endo	N	N	N	N	NF for endo	N	N	N	NF	N
Duration limitations (# of months)	NF for endo	N	NF for endo	N	N	N	N	NF for endo	N	N	N	NF	N
Specialty	NF for endo	N	NF for endo	N	N	N	N	NF for endo	N	N	N	NF	N
Anastrozole (Trademark: Arimidex; Manufacturer: AstraZeneca)													
Tier	1	1	2	2	1	1	1	2	2	1	1	NF	1
PA	N	N	N	N	N	N	N	N	N	N	N	NF	N
Diagnosis or pre-treatment by a specialist	N	N	N	N	N	N	N	N	N	N	N	NF	N
Duration limitations (# of months)	N	N	N	N	N	N	N	N	N	N	N	NF	N
Specialty	N	N	N	N	N	N	N	N	N	N	N	NF	N
NF=Non Formulary; MD=Medical Benefit													

Appendix C. Previous Systematic Reviews and Technology Assessments

GnRH analogues

We identified one systematic review of GnRH agonists (2010) for pain associated with endometriosis. [12]. The clinical evidence was summarized from 41 RCTs, which included 4,742 women. The review determined the overall quality of the trials as reasonable.[12]

The evidence supported GnRH agonists as more effective at symptom relief compared to placebo or no treatment. Compared with danazol, there was no statistically significant difference in pain relief and more adverse events in the GnRH agonist groups. The authors also found no evidence of difference in pain relief between GnRH agonists and levonorgestrel and no studies that compared GnRH agonists with analgesics. Lastly, the authors determined that the evidence was too limited to reach conclusions regarding the benefits of different GnRH agonists doses or length of treatment.

Oral contraceptives

We identified one Cochrane systematic review, published in 2009, on oral contraceptive pills in comparison to other treatments for endometriosis-related pain in women of reproductive age.[82] Only one small trial (57 women) compared oral contraceptives to goserelin, a GnRH agonist.

The results were comparable between oral contraceptives and goserelin in treating nonmenstrual pain.[82] However, goserelin was more effective at treating dysmenorrhea, menstrual pain.[82] All patients in both treatment groups experienced recurring symptoms six months after stopping treatment. No patient in either group had experienced complete resolution of dysmenorrhea six months after treatment. Further, there was no statistical difference in dyspareunia between the oral contraceptives and goserelin, either at the end of treatment or after six months follow up.

Goserelin was associated with more reported side effects, such as hot flushes, vaginal dryness, and insomnia, and it can only be taken for six months at a time.

Progestogens

We identified one Cochrane systematic review, published in 2012, on the effectiveness of both progestogens and anti-progestogens in treating endometriosis-related pain symptoms.[83]

The authors reviewed evidence from 13 RCTs which included 1,551 women and compared progestogens with placebo, danazol, oral or subdermal contraceptive, oral contraceptive pill and danazol, GnRH analogue and other drugs. Only six of the 13 studies included in the review adequately described randomization and allocation concealment. Since there were limited studies for each comparison, the applicability of the data was limited.

For the two studies that compared oral progestogens with placebo, only one identified a benefit for reducing symptoms.[83] The other trial showed no significant difference between progestogen and placebo.[83]

The progestogen groups were associated with more adverse events, including acne, edema, headaches, and cycle irregularity. There was no evidence to suggest a benefit for depot or oral administration of progestogens compared with other forms of treatment. For anti-progestogens, there was no evidence to show a benefit in reducing symptoms when compared with danazol.[83] Furthermore, one trial found a GnRH analogue (leuprorelin) superior to an anti-progestogen.[83]

Aromatase inhibitors

We identified one systematic review of aromatase inhibitors (2008) in treating endometriosis-related pain.[44] There were eight studies (137 women) included in the review; four cases reports, three observational studies and one RCT. The review found that aromatase inhibitors had promising, but unproven, clinical effects in alleviating pain, reducing lesion size, and possibly improving quality of life associated with endometriosis.[44]

The overall quality of included studies was poor due to the study design and limited number of women. Moreover, aromatase inhibitors were often used together with progestogens, oral contraceptives, or GnRH analogues. The results of the reports showed that the combination of aromatase inhibitors and active medication reduced mean pain scores, lesion size and improved quality of life.[44]

The RCT demonstrated that aromatase inhibitors combined with a GnRH agonist significantly improved pain scores and 24-month post-medical therapy multidimensional scores, compared with GnRH agonist alone. From a safety standpoint, the results from these studies suggested that aromatase inhibitors had a nonsignificant reduction in bone mineral density of the spine and hip.[44]

Appendix D. Ongoing Studies

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Primary Completion Date

A Clinical Study to Evaluate the Safety and Efficacy of Elagolix in Participants With Moderate-to-Severe Endometriosis-Associated Pain
 	
Abbvie
 	
NCT03213457
	Phase III
	
	RCT
	
	Double-blind
	
	Estimated Enrollment: 700
		1. Elagolix (twice daily) + Estradiol/ Norethindrone Acetate (once daily)
		
		2. Elagolix (twice daily) + Placebo
		
		3. Placebo
			Inclusion Criteria
			• Premenopausal female age 18-49
			• Surgical diagnosis of endometriosis within previous 10 years
			• During the last 35 days:
			  • ≥2 days of "moderate" or "severe" Dysmenorrhea AND either
			  • ≥2 days of "moderate" or "severe" Nonmenstrual pelvic pain (NMPP) and average NMPP score of ≥1.0, OR
			  • ≥4 days of "moderate" or "severe" NMPP and an average NMPP score of ≥0.5.
			Exclusion Criteria
			• Chronic pelvic pain not caused by endometriosis
			• Systemic corticosteroid use over 14 days within 3 months of screening
			• History of major depression or PTSD
			• Osteoporosis or other metabolic bone disease
			• BMD <2.0 SD of lumbar spine, femoral neck, or hip
			• Clinically significant medical condition requiring therapeutic intervention
				Primary Outcome Measures
				• Proportion of responders based on Dysmenorrhea [month 6]
				• Proportion of responders based on nonmenstrual pelvic pain [month 6]
				
				Secondary Outcome Measures
				Change from baseline:
				• Dysmenorrhea
				• Dyspareunia
				• Analgesic use
				• Numeric rating scale
				• Nonmenstrual pelvic pain
					October 29, 2018

Title, Trial Sponsor, ClinicalTrials.gov Identifier	Study Design	Treatment Arms	Patient Population	Key Outcomes	Estimated Primary Completion Date
A Study to Evaluate Safety and Efficacy of Elagolix in Participants With Endometriosis With Associated Moderate-to-Severe Pain AbbVie NCT03343067	Phase III RCT Double-blind Estimated Enrollment: 890	*Incomplete efficacy responders to elagolix dose A at Month 3 randomized to* (1.) continue dose A up to 24 months if responding at month 6, (2.) increase to elagolix dose B plus E2/NETA through Month 24 if have incomplete response at month 6, (3.) switch to elagolix dose B + E2/NETA at Month 3, or (4.) *Efficacy responders to elagolix dose A at Month 3 continue therapy*	Inclusion Criteria • Premenopausal female age 18-49 • Documented surgical diagnosis within 10 years of study entry • Agree to use only permitted rescue analgesics for pain • During the last 35 days: • ≥2 days of "moderate" or "severe" Dysmenorrhea AND either • ≥2 days of "moderate" or "severe" Nonmenstrual pelvic pain (NMPP) and an average NMPP score of ≥1.0, OR • ≥4 days of "moderate" or "severe" NMPP and an average NMPP score of ≥0.5. Exclusion Criteria • Chronic pelivic pain not caused by endometriosis • Systemic corticosteroid use for >14 days within 3 months prior to study • History of major depression or PTSD • BMD <2.0 SD of lumbar spine, femoral neck, or hip • Clinically significant medical condition requiring therapeutic intervention and contraindicated with use of E2/NETA	Primary Outcome Measures • Proportion of responders based on nonmenstrual pelvic pain [month 6] • Proportion of responders based on dysmenorrhea [month 6] • Bone Mineral Density evaluation [up to month 24] Secondary Outcome Measures *Change from baseline:* • Daily Diary endometriosis-associated pain score • Rescue analgesic use • Percentage of participants with reduction in endometriosis-associated pain score • Nonmenstrual pelvic pain • Dysmenorrhea • Dyspareunia	October 18, 2021

Appendix E. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We did not have any FDA documents to review related to elagolix.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[56] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

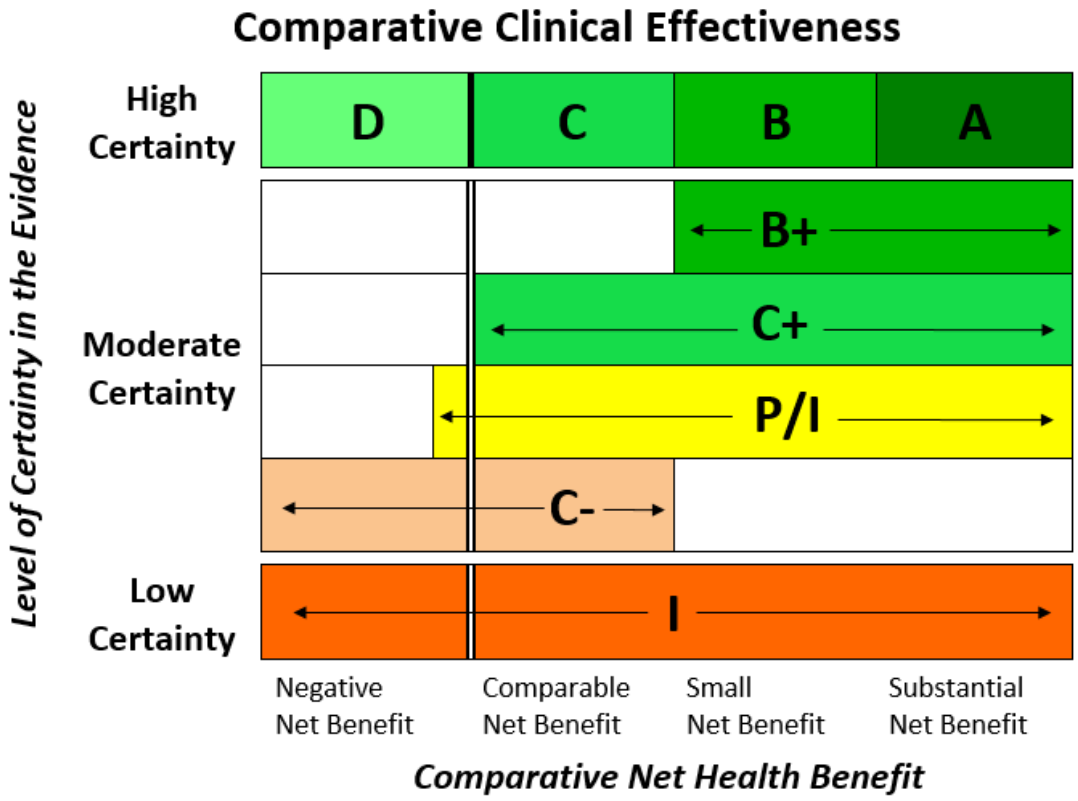
Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality.

ICER Evidence Rating Matrix

We used the ICER Evidence Rating Matrix (see Figure E1) to evaluate the evidence for a variety of outcomes.[57] The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.

Figure E1. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D = "Negative"- High certainty of an inferior net health benefit
B+ = "Incremental or Better" - Moderate certainty of a small or substantial net health benefit, with high certainty of at least a small net health benefit
C+ = "Comparable or Better" - Moderate certainty of a comparable, small, or substantial net health benefit, with high certainty of at least a comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a comparable, small, or substantial net health benefit, and a small (but nonzero) likelihood of a negative net health benefit
C- = "Comparable or Inferior" - Moderate certainty that the point estimate for comparative net health benefit is either comparable or inferior
I = "Insufficient" - Any situation in which the level of certainty in the evidence is low

Clinical Effectiveness of Comparators versus Placebo

Table E1. Pain Measures from Placebo-Controlled Comparator Trials

Comparator Trials	F/U Duration	Treatment Groups	Patient Characteristics	Primary Outcome
Dlugi, 1990	6 months	Placebo Leuprorelin acetate depot 3.75 mg IM	N=63 Mean age: 30 Age range: 19-44 BMI (kg/m^2): 24*	B&B scale: DYS, NMPP, dyspareunia, pelvic tenderness
Ling, 1999	3 months	Placebo Leuprorelin acetate depot 3.75 mg IM	N=100 Mean age placebo: 29.4ǂ Mean age LA: 32.3ǂ Caucasian: 76% BMI (kg/m^2): NR	B&B scale, physician assessed monthly; NRS/VAS DYS, NMPP and dyspareunia patient assessed monthly analog scale
Harada, 2008	3 months	Placebo Ethinylestradiol (0.035 mg) plus norethisterone (1 mg) (OCP)	N=100 Mean age: 31.6 (SD 5.9) Caucasian: 0% (100% Japanese) BMI (kg/m^2): NR	Modified B&B for DYS. Also measured DYS and NMPP by VAS; pelvic induration by physician

*BMI calculated from height and weight means. ǂ Difference between arms is statistically significant (p=0.036). f/u= follow-up; QD=daily; BID= twice a day; BMI=body mass index; NRS=numeric rating scale (0-10); B&B= Biberoglu and Behrman (0-3); VAS=visual analog scale (1-100)

Leuprorelin Acetate (LA)

We searched two recent systematic reviews for placebo-controlled trials of FDA-approved GnRH agonists for inclusion in our review.[21,55] We identified two studies that were published in the 1990s.[32,33] These studies are summarized below (see "Additional Evidence on GnRH Agonists").

Dlugi et al., was a phase III, double-blind, placebo-controlled trial that randomized 63 women to leuprolide acetate (LA) or placebo.[32] The study was conducted at 11 sites in the US and similar to the elagolix trials included women 18 and older with moderate or severe endometriosis-related pain and a definitive diagnosis by laparoscopy. The primary endpoint of the trial was reduction in dysmenorrhea, pelvic pain, dyspareunia and pelvic tenderness at six months. Due to eligibility violations and high drop-out rates (approximately 90% in the placebo arm), the study does not provide a valid comparison of LA to placebo; however, in the 24 women randomized to LA that were followed-out to one year, 57% reported return of dysmenorrhea six months following cessation of treatment while 33% reported ongoing benefits (no magnitude or significance provided).[32]

Ling et al., performed a double-blind trial of 100 women randomized to treatment with depot leuprolide (3.75 mg IM) or placebo in a 1:1 fashion using block randomization.[33] The study was conducted at 12 sites in the United States between June 1995 and January 1997 and enrolled

women ages 18-45 years with moderate-to-severe chronic pelvic pain of at least six months.[33] Unlike trials of elagolix, women did not need a laparoscopic diagnosis to enroll in this study. The primary endpoint was physician-reported reduction in pain at three months. Patient-reported pain was a secondary endpoint. Some baseline characteristics were imbalanced. Women in the LA arm were older than women in the placebo arm (p=0.036) and the mean pelvic pain score was greater in the LA arm than the placebo arm at baseline (p=0.017).[33]

The B&B scale (0-4 rating) was used to measure physician-rated pain (dysmenorrhea, nonmenstrual pelvic pain and deep dyspareunia) as well as pelvic tenderness and induration which were assessed through a pelvic exam at all study visits. Assuming 80% power, a 0.51-point difference in B&B score between arms was considered to be a statistically significant finding. Patient-reported pain (dysmenorrhea, nonmenstrual pelvic pain and deep dyspareunia) were assessed at baseline and monthly using a 0-10 visual analog scale. The McGill Pain Questionnaire to measure overall pelvic pain was also utilized. The McGill Pain Score has three sections: what does your pain feel like, how does your pain change with time, and how strong is your pain. [84] The scores range from zero (no pain) to 78 (highest pain).[84]

There were no discontinuations due to adverse events in either arm. Only B&B measures aligned with trials of elagolix. At three months, patient-reported pain also clinically and statistically favored leuprolide over placebo (visual analog scale results ranged from -3.1 for dyspareunia to -6.3 for dysmenorrhea).[33] All women in the LA arm saw physician-evaluated dysmenorrhea score reductions.[33,55] Across all five domains of the B&B, there was statistically significant reductions in physician-evaluated pain at three months favoring leuprolide over placebo (mean differences ranged from -0.7 for pelvic induration to -1.7 for dysmenorrhea).[33] Differences in mean total McGill pain scores were also statistically different with lower pain reported in the leuprolide arm.[33]

After the primary endpoint data was collected, researchers performed laparoscopy to assess the presence of endometriosis in each arm in the study. Post-treatment laparoscopy showed that only 78% of women randomized to LA had laparoscopic evidence of endometriosis versus 87% of women in the placebo arm.[33] Among those with diagnoses, 82% of women experienced pain relief after three months with leuprolide whereas 39% of women taking placebo found pain relief (placebo response).[33] For those who did not have laparoscopic evidence of endometriosis, 73% who received leuprolide reported pain relief at three months compared with 17% randomized to placebo.[33]

Analgesic use and quality of life measures were not reported in the Ling study.

Hormonal Contraceptives

No studies were identified that compared DMPA-SC to placebo. As noted above, we identified one randomized, double-blind, multicenter trial of monophasic ethinylestradiol plus norethisterone

(OCP) versus placebo.[58] The study was conducted at 18 centers in Japan and enrolled 100 women over the age of 18 with moderate-to-severe dysmenorrhea.[58] Women could be diagnosed surgically or have an ovarian endometrioma diagnosed by imaging. Ninety-six percent of women in the OCP and 94% of women in the placebo group had an endometrioma.[58] The primary endpoint was patient response to treatment for dysmenorrhea associated by VAS at four months.[58]

Changes in dysmenorrhea and NMPP were measured through a verbal rating scale (VRS) of 0 to 3 using pain as a proxy for ability to work (0-none, 1-mild with some loss of work, 2-moderate with rest in bed, 3- severe with one or more days in bed).[58] The investigators also collected dysmenorrhea and nonmenstrual pelvic pain using a VAS (0-100).[58]

Total dysmenorrhea scores by VRS were decreased in both arms but the difference between OCP and placebo was statistically significant in favor of OCP (-2.0 vs. -0.6; $p<0.0001$).[58] Mean VAS dysmenorrhea scores followed the same pattern.[58] Nonmenstrual pelvic pain scores did not differ between arms.[58] Dyspareunia was not reported.

Harada captured analgesic use with a zero to three rating score: no analgesics (0=none) to greater than three per day (3=severe); however, data on the change from baseline to four months were not provided. The discussion section of the manuscript stated that days of analgesic use declined but no quantification was provided.[58]

Quality of life was not measured in Harada et al.[58]

Aromatase Inhibitors

As noted in Section 3.3 of the report, our literature search did not identify any studies of aromatase inhibitors versus elagolix or placebo. However, we identified one systematic review of these agents for endometriosis pain, which we summarize below for context.

The systematic review of aromatase inhibitors for endometriosis included evidence from four case reports (total n=5), two nonrandomized pilot studies (total n=20), one prospective Phase II nonrandomized study (n=15) and one RCT of a GnRH agonist (goserelin) plus anastrozole compared to goserelin alone (n=97).[44]

In these studies, endometriosis-related pain was reduced with the use of an aromatase inhibitor in combination with hormonal treatments or a GnRH agonist.[44,85] Bone mineral density loss was not consistently demonstrated across studies included in the review, although the authors acknowledged that they were limited by poor quality evidence (i.e., small sample sizes and risk of bias).[44,85] We did not identify any studies relevant to our review that were published subsequent to this systematic review.

Evidence Tables

Table E2. Evidence Tables

Author & Year of Publication Trial Name Quality Rating	Study Design and Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Taylor HS 2017[24] **NEJM** **Elaris EM-I** **Good**	Parallel group, double-blind, randomized, 6-month phase III trial. 151 sites in the US and Canada from July 2012 through May 2014. Duration of follow up: 18 months (6-month randomized period, with a follow-up period up to 12 months) Sponsored by industry	**N=872** (1) Placebo (n=374) (2) Elagolix 150 mg: once daily (n=249) (3) Elagolix 200 mg: twice daily (n=248) Randomization 3:2:2 **Patients who completed the trial, n (%)** (1) 274 (73) (2) 196 (79) (3) 183 (74)	**Inclusion** • Premenopausal woman ages 18-49 years • Diagnosed with endometriosis within 10 years of study entry • Moderate or severe endometriosis-associated pain **Exclusion:** • Women were pregnant, breast feeding, planning a pregnancy within the next 24 months, or less than 6 months post-partum, post-abortion, or post-pregnancy • With a history of previous non-response to gonadotropin-releasing hormone agonists, antagonists, DMPA, aromatase inhibitors	**Age, yrs Median [range]** (1) 31 [18-48] (2) 32 [19-48] (3) 31 [18-47] **BMD (SD)** (1) 28 (6) (2) 28 (6) (3) 28 (6) **NMPP (SD)** (1) 1.6 (0.5) (2) 1.6 (0.5) (3) 1.6 (0.5) **DYS (SD)** (1) 2.2 (0.4) (2) 2.2 (0.5) (3) 2.2 (0.5) **Dyspareunia(SD)** (1) 1.5 (0.8) (2) 1.5 (0.8) (3) 1.6 (0.9) **NRS (SD)** (1) 5.6 (1.6) (2) 5.7 (1.7) (3) 5.5 (1.6)	**Response *DYS, %*** 6 months: (1) 23.1 (2) 42.1 (3) 75.3 ***Response NMPP, %*** 6 months: (1) 34.9 (2) 45.7 (3) 62.1 **NRS Mean chg (SE)** 3 months: (1) -1.09 (0.10) (2) -1.74 (0.12) (3) -2.39 (0.12) **DYS Mean chg (SE)** 6 months: (1) -0.44 (0.05) (2) -0.89 (0.06) (3) -1.75 (0.06) **NMPP Mean chg (SE)** 6 months: (1) -0.31 (0.04) (2) -0.48 (0.04) (3) -0.72 (0.04) **Dyspareunia chg (SE)** 3 months: (1) -0.29 (0.04) (2) -0.39 (0.05) (3) -0.49 (0.05)	**SAEs, n (%)** (1) 12 (3.2) (2) 2 (0.8) (3) 7 (2.8) **Discontinuation d/t AE, n (%)** (1) 22 (5.9) (2) 16 (6.4) (3) 23 (9.3) **Hot flush, n (%)** (1) 26 (7.0) (2) 59 (23.7) (3) 105 (42.3) **Headache, n (%)** (1) 37 (9.9) (2) 38 (15.3) (3) 43 (17.3) **Nausea, n (%)** (1) 51 (13.6) (2) 25 (10.0) (3) 40 (16.1) **BMD, % change** ***Lumbar spine*** (1) 0.47 (2) -0.32 (3) -2.61 ***Femoral neck*** (1) 0.02 (2) -0.39 (3) -1.89

Author & Year of Publication Trial Name Quality Rating	Study Design and Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Taylor HS 2017[24] **NEJM** **Elaris EM-II** **Good**	Parallel group, double-blind, randomized, 6-month phase III trial. Multiple sites in the US, UK, European countries, Argentina, and South Africa. Duration of follow up: 12 months (additional 6 month open-label phase if patients wanted) Sponsored by industry	**N=815** (1) Placebo (n=360) (2) Elagolix 150 mg: once daily (n=226) (3) Elagolix 200 mg: twice daily (n=229) Randomization 3:2:2 **Patients who completed the trial, n (%)** (1) 270 (75) (2) 178 (79) (3) 184 (80)	**Inclusion** • Premenopausal woman ages 18-49 years • Diagnosed with endometriosis within 10 years of study entry • Moderate or severe endometriosis-associated pain **Exclusion:** • Women were pregnant, breast feeding, planning a pregnancy within the next 24 months, or less than 6 months post-partum, post-abortion, or post-pregnancy • With a history of previous non-response to gonadotropin-releasing hormone agonists, antagonists, DMPA, aromatase inhibitors	**Age, yrs** **Median [range]** (1) 33 [18-49] (2) 33 [20-49] (3) 34 [18-47] **BMD (SD)** (1) 27 (6) (2) 27 (7) (3) 27 (7) **NMPP (SD)** (1) 1.6 (0.5) (2) 1.7 (0.5) (3) 1.6 (0.5) **DYS (SD)** (1) 2.2 (0.5) (2) 2.2 (0.5) (3) 2.1 (0.5) **Dyspareunia(SD)** (1) 1.5 (0.8) (2) 1.5 (0.9) (3) 1.4 (0.9) **NRS (SD)** (1) 5.6 (1.8) (2) 5.7 (1.8) (3) 5.3 (1.8)	**Patients response** ***DYS, %*** 6 months: (1) 25.4 (2) 46.2 (3) 76.9 ***NMPP, %*** 6 months: (1) 40.6 (2) 51.6 (3) 62.2 **NRS Mean chg (SE)** 3 months: (1) -1.33 (0.10) (2) -1.90 (0.12) (3) -2.55 (0.12) **DYS Mean chg (SE)** 6 months: (1) -0.52 (0.05) (2) -1.06 (0.06) (3) -1.65 (0.06) **NMPP Mean chg (SE)** 6 months: (1) -0.48 (0.04) (2) -0.63 (0.04) (3) -0.80 (0.04) **Dyspareunia chg (SE)** 3 months: (1) -0.30 (0.04) (2) -0.39 (0.05) (3) -0.60 (0.05)	**SAEs, n (%)** (1) 12 (3.3) (2) 12 (5.3) (3) 5 (2.2) **Discontinuation d/t AE, n (%)** (1) 22 (6.1) (2) 10 (4.4) (3) 23 (10.0) **Hot flush, n (%)** (1) 37 (10.3) (2) 51 (22.6) (3) 109 (47.6) **Headache, n (%)** (1) 51 (14.2) (2) 42 (18.6) (3) 52 (22.7) **Nausea, n (%)** (1) 41 (11.4) (2) 26 (11.5) (3) 36 (15.7) **BMD, % change** ***Lumbar spine*** (1) 0.56 (2) -0.72 (3) -2.49 ***Femoral neck*** (1) 0.31 (2) -0.35 (3) -1.42

Author & Year of Publication Trial Name Quality Rating	Study Design and Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
E. Surrey 2018[26] **Obstetrics & Gynecology** **Elaris EM-III** **Elaris EM-IV**	**Design see EM-I and EM-II** EM-III and EM-IV are two extension studies of EM-I and EM-II. Overall treatment period: 12 months (additional 6 month for EM-III & EM-IV) Post-treatment follow-up: 12 months Due to enrollment timing in EM-III and EM-IV, some women received more than 12 months of treatment. Sponsored by industry	**EM-III (**N=287) (1) Elagolix: 150 mg once daily n=116 completed=114 (2) Elagolix: 200 mg twice/d n=115 completed=108 **EM-IV (**N=282) (1) Elagolix: 150 mg once daily n=127 completed=122 (2) Elagolix: 200 mg twice/d n=121 completed=111	**See EM-I and EM-II**	**EM-III:** **Age, yrs** **Mean (range)** (1) 32 (19-48) (2) 31 (18-47) **BMI, kg/m²** **Mean (SD)** (1) 28.8 (6.4) (2) 28.3 (6.5) **Use of opioids only, %** (1) 18.1 (2) 18.8 **Percentage of white, %** (1) 89.3 (2) 91.3 **EM-IV:** **Age, yrs** **Mean (range)** (1) 33 (20-48) (2) 34 (18-47) **BMI, kg/m²** **Mean (SD)** (1) 26.5 (6.3) (2) 26.9 (6.5) **Use of opioids only, %** (1) 17.6 (2) 10.7 **Percentage of white, %** (1) 89.4 (2) 90.0	12 months Response **DYS, n (%)** EM-III: (1) 61 (52) (2) 86 (78) EM-IV: (1) 62 (51) (2) 88 (76) **NMPP, n (%)** EM-III: (1) 79 (68) (2) 76 (69) EM-IV: (1) 81 (66) (2) 78 (67) **Dyspareunia, n (%)** EM-III: (1) 38 (45) (2) 42 (60) EM-IV (1) 39 (46) (2) 43 (58)	**Hot flush, n (%)** EM-III: (1) 6 (4.0) (2) 8 (5.8) EM-IV: (1) 7 (4.9) (2) 11 (7.9) **Depression n (%)** EM-III: (1) 8 (5.4) (2) 4 (2.9) EM-IV: (1) 1 (0.7) (2) 0 (0) **BMD decrease >5%, <8%, N (%)** EM-III: (1) 3 (2.6) (2) 28 (26) EM-IV: (1) 4 (3.3) (2) 33 (30) **BMD decrease ≥ 8%, N (%)** EM-III: (1) 1 (0.9) (2) 14 (13) EM-IV: (1) 1 (0.8) (2) 13 (12)

Author & Year of Publication Trial Name Quality Rating	Study Design and Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
B. Carr 2014[25] **Reproductive Sciences** **Fair**	Parallel group, double-blind, randomized, 24-week, phase II trial. Multiple centers in the US from December 2006 to November 2008. Duration of follow up: 48 weeks Sponsored by industry	**N=252** (1) DMPA-SC: 104mg/0.65mL daily (n=84) (2) Elagolix 150 mg: once daily (n=84) (3) Elagolix 75 mg: twice daily (n=84) Randomization 1:1:1	**Inclusion** • Premenopausal woman ages 18-49 years • Diagnosed with endometriosis within 10 years of study entry • Moderate or severe endometriosis-associated pain • At least 7 days of e-Diary entries prior to randomization **Exclusion** • Had been administered a GnRH agonist or antagonist, danazol, or DMPA within 12 months of screening • History of unresponsiveness to GnRH agonist or antagonist therapy • Had a BMD with either lumbar spine of femur T-scores below -1.5 at screening	**Age, yrs** **Mean (SD)** (1) 31.6 (0.4) (2) 32.4 (0.8) (3) 31.4 (0.7) **BMI, kg/m²** **Mean (SD)** (1) 26.2 (0.5) (2) 26.5 (0.5) (3) 25.4 (0.5) **Use of opioids only, %** (1) 28.9 (2) 21.4 (3) 19.0 **Percentage of white, %** (1) 77.4 (2) 81.0 (3) 83.3	**Patients response** ***DYS, %*** 24 weeks: (1) 86.3 (2) 86.0 (3) 73.8 ***NMPP, %*** 24 weeks: (1) 76.5 (2) 86.0 (3) 76.9 **BMD, *24 weeks:*** ***Spine,* % (95%CI)** (1) -0.99 (-1.61, -0.37) (2) -0.11 (-0.70, 0.48) (3) -1.29 (-1.85, -0.74) ***Femur,* % (95%CI)** (1) -1.29 (-1.80, -0.77) (2) -0.47 (-0.96, 0.02) (3) -1.02 (-1.48, -0.56) **VAS, pelvic pain (SE)** 24 weeks: (1) -17 (3.9) (2) -18.2 (3.2) (3) -23.6 (3.0) **Use rescue opioids, %** 24 weeks: (1) 33.7 (2) 23.8 (3) 25.0	**SAEs, n** 24 weeks: (1) 3 (2) 1 (3) 2 **Discontinuation d/t AE, %** 24 weeks: (1) 16.7 (2) 4.8 (3) 8.3 **Headache, n (%)** 24 weeks: (1) 15 (17.9) (2) 22 (26.2) (3) 23 (27.4) **Nausea, n (%)** (1) 13 (15.5) (2) 16 (19.0) (3) 13 (15.5) **Nasopharyngitis, n (%)** (1) 9 (10.7) (2) 9 (10.7) (3) 18 (21.4)

Author & Year of Publication Trial Name Quality Rating	Study Design and Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Diamond 2014[25] **Reproductive Sciences** **Fair**	Parallel group, randomized, double-blind, phase II trial. 50 US centers from February 2008 to August 2009. Duration of follow up: 30 weeks (Placebo patients randomized to elagolix after 12 weeks, and elagolix patients continued for additional 12 weeks) Sponsored by industry	**N=155** (1) Placebo (n=52) (2) Elagolix 150 mg: once daily (n=51) (2) Elagolix 250 mg: once daily (n=52) Randomization 1:1:1 Patients who completed randomized period: **N=102**	**Inclusion** • Women aged 18 to 49 years, with a laparoscopically diagnosis of endometriosis • Moderate-to-severe endometriosis-related pain • Randomized patients also agreed to use two forms of non-hormonal contraception during the study **Exclusion** • Administered a GnRH agonist, a GnRH antagonist, or danazol within 6 months of screening, depot medroxyprogesterone acetate within 3 months of screening, or had used hormonal contraception or other hormonal therapy within 1 month of screening	**Age, yrs** **Mean (SE)** (1) 31.2 (1.0) (2) 30.9 (1.0) (3) 31.0 (1.0) **BMI, kg/m²** **Mean (SE)** (1) 26.7 (0.7) (2) 27.3 (0.7) (3) 27.3 (0.8) **Percent days with prescription analgesic use, %** (1) 10.0 (2) 10.0 (3) 7.0 **Percentage of white, %** (1) 82.7 (2) 82.4 (3) 78.8	**DYS score (digitized)** **Mean change (SE)** 3 months: (1) -0.20 (0.10) (2) -0.78 (0.10) (3) -0.78 (0.10) **NMPP (digitized)** **Mean change (SE)** 3 months: (1) -0.34 (0.20) (2) -0.32 (0.30) (3) -0.25 (0.30) **Dyspareunia(digitized)** **Mean change (SE)** 3 months: (1) -0.61 (0.20) (2) -1.09 (0.10) (3) -0.69 (0.20) **NRS** **Mean change (SE)** 3 months: (1) -0.88 (0.18) (2) -1.19 (0.18) (3) -1.25 (0.18) **Percent days with prescription analgesic use (SD)** (1) -2.1 (1.6) (2) -2.6 (1.6) (3) -3.3 (1.6)	**Discontinuation d/t AE, n (%)** 3 months: (1) 0 (0) (2) 1 (1.9) (3) 4 (7.7) **BMI, mean change (SD)** 3 months: (1) 0.375 (2.10) (2) -0.0045(2.09) (3) -0.937 (2.75) **Headache, n (%)** 3 months: (1) 1 (1.9) (2) 5 (9.8) (3) 4 (7.7) **Nausea, n (%)** 3 months: (1) 1 (1.9) (2) 5 (9.8) (3) 3 (5.8) **Anxiety n (%)** 3 months: (1) 0 (0) (2) 3 (5.9) (3) 3 (5.8)

Author & Year of Publication Trial Name Quality Rating	Study Design and Duration of Follow-Up	Interventions (n) & Dosing Schedule	Major Inclusion & Exclusion Criteria	Patient Characteristics	Key Outcomes	Harms
Acs N. 2014[22] **JEPD** **Fair**	Parallel group, randomized, double-blind, 12-week phase II trial. Multiple centers in Bulgaria, Hungary, Poland, Romania, Russian Federation, Ukraine Duration of follow up: 24 weeks Patients who were randomized to placebo or leuprorelin were re-randomized to elagolix at week 12.	**N=174** (1) Placebo: for 12 weeks (n=43) (2) Leuprorelin acetate: 3.75 mg monthly for 12 weeks (n=44) (3) Elagolix 150 mg: once daily (n=43) (4) Elagolix 250 mg: once daily (n=44) **Patients who completed the trial, %** (1) 40 (2) 42 (3) 38 (4) 41	**Inclusion** • Women aged 18 to 49 years, with a laparoscopically diagnosis of endometriosis • Moderate-to-severe endometriosis-related pain **Exclusion** • Excluded if patients were administered a GnRH agonist or antagonist, or danazol within 6 months of screening, depot medroxyprogesterone acetate within 3 months of screening • Had used hormonal contraception or other hormonal therapy within 1 month of screening • Had a history of unresponsiveness to GnRH agonist or antagonist treatment	**Mean age of the total study population:** 31.7 years **Mean BMI of the total study population:** 22.6 kg/m^2 **NMPP, mean** (1) 1.0 (2) 0.9 (3) 1.1 (4) 0.9 **DYS, mean** (1) 1.4 (2) 1.3 (3) 1.3 (4) 1.1 **NRS, mean** (1) 3.3 (2) 3.1 (3) 3.7 (4) 3.3 **Days with analgesic use, % (SD)** (1) 14.2 (3.1) (2) 10.0 (2.1) (3) 15.1 (3.1) (4) 11.7 (2.4)	**NRS (digitized) Mean change (SE)** <u>3 months:</u> (1) -1.2 (0.5) (2) -1.7 (0.3) (3) -1.5 (0.4) (4) -1.5 (0.3) **DYS score (digitized) Mean change (SE)** <u>3 months:</u> (1) -0.5 (0.1) (2) -1.2 (0.1) (3) -0.8 (0.1) (4) -0.8 (0.1) **NMPP (digitized) Mean change (SE)** <u>3 months:</u> (1) -0.3 (0.1) (2) -0.5 (0.1) (3) -0.4 (0.1) (4) -0.3 (0.9) **Use of rescue analgesic agent Mean change (SD)** <u>3 months:</u> (1) -6.2 (2.0) (2) -10.5 (2.0) (3) -4.4 (2.0) (4) -8.3 (2.0)	**Discontinuation d/t AE, n (%)** <u>3 months:</u> (1) 0 (0) (2) 0 (0) (3) 2 (4.7) (4) 1 (2.3) **Headache, n (%)** <u>3 months:</u> (1) 2 (4.7) (2) 6 (13.6) (3) 8 (18.6) (4) 4 (9.1) **Nausea, n (%)** <u>3 months:</u> (1) 1 (2.3) (2) 0 (0) (3) 3 (7.0) (4) 2 (4.5) **BMI, g/cm^2 Mean chng (SD)** ***Spine*** (1) 0.106(1.893) (2) -1.633(2.113) (3) -1.053(1.985) (4) -0.799(2.352) ***Femur*** (1) -0.90 (1.316) (2) -1.122(1.634) (3) -0.342(1.583) (4) -0.562(1.367)

Appendix F. Comparative Value Supplemental Information

Table F1. Impact Inventory

Sector	Type of Impact	Included in this Analysis from Perspective	
		Health Care Sector	Societal
Health Outcomes	Longevity effects	✓	✓
	Health-related quality of life effects	✓	✓
	Adverse events	✓	✓
Medical Costs	Paid by third-party payers	✓	✓
	Paid by patients out-of-pocket	✓	✓
	Future related medical costs	✓	✓
	Future unrelated medical costs	☐	☐
Health-Related Costs	Patient time costs	☐	✓
	Unpaid caregiver-time costs	☐	☐
	Transportation costs	☐	☐
Productivity	Labor market earnings lost	☐	✓
	Cost of unpaid lost productivity due to illness	☐	☐
	Cost of uncompensated household production	☐	☐
Consumption	Future consumption unrelated to health	☐	☐
Social services	Cost of social services as part of intervention	☐	☐
Legal/Criminal Justice	Number of crimes related to intervention	☐	☐
	Cost of crimes related to intervention	☐	☐
Education	Impact of intervention on educational achievement of population	☐	☐
Housing	Cost of home improvements, remediation	☐	☐
Environment	Production of toxic waste pollution by intervention	☐	☐
Other	Other impacts (if relevant)	☐	☐

Model Parameters

Health Care Utilization Costs

Costs associated with healthcare utilization that result from surgical procedures and long-run adverse events from treatment of endometriosis were included in the model. Table 4.10 details the healthcare utilization unit costs that were used in the model. Unit costs for healthcare utilization were the same across different treatments and populations.

Table F2. Mean Healthcare Costs per Patient Receiving Treatment

Input	Value	Source
Laparoscopic Surgery (Cycle Length Cost)	$11,959	[7]
Hysterectomy (Cycle Length Cost)	$16,421	[7]
Outpatient Visits	$74.16	Physician Fee Schedule[86]

All costs inflated to 2018 U.S dollars.

Adverse Events

Given the trial for elagolix did not reveal any serious grade 3/4 adverse events, the model focused on estimating the impact of changes in clinical markers from elagolix and comparator treatment on long-run adverse events. Long-run adverse event model parameters are shown in Table 4.6. Specifically, fracture risk and cardiovascular disease were both modeled beginning at 40 and 32 years of age, respectively.[87,88] The model applied a cost to treat fractures and a disutility to the proportion of women with low bone mineral density from elagolix and the comparator. Patients on elagolix had an increased risk of fractures based on low bone mineral density. The model separately applied a cost and disutility to manage cardiovascular disease for elagolix and the comparator. The model did not apply an increased risk of mortality from fractures or cardiovascular disease.

Table F3. Risks of Long-Term Adverse Events Included in Model

Adverse Event	Elagolix 200 mg Twice Daily[a]	No Active Treatment	Source
Proportion of Women with Low Bone Mineral Density on Treatment (-1.5 Z Score or Less)	0.041	0.002*	Taylor et al., 2017[24]
Relative Risk of Fracture with A 1 SD Decrease in Bone Mineral Density (i.e., Low Bone Mineral Density)	1.5 (1.36, 1.65)		Kanis et al., 2001[88]
Osteoporotic Fracture Risk for Normal Bone Density (Women Aged 40-49 Years)[b]	0.00065 (0.00063, 0.00067)		Looker et al., 2017[89]
Probability of Cardiovascular Disease[b,c]	0.00016	0.00015	D'Agostino et al., 2008[87]

[a] Risk inputs are varied in sensitivity analyses if confidence intervals listed
[b] 3-month cycle length probabilities
[c] Risk calculation based on average lipid panels at end of trial for each group; lower and upper lipid panel values are varied in sensitivity analyses
*No Active Treatment refers to placebo response in the EM-I and EM-II trials

Treatment Disutilities

Disutilities were applied for the proportion of women developing long-run adverse events. Table F4 details the disutilities applied for each adverse event. The utility of cardiovascular disease was

subtracted from the overall utility of the proportion with cardiovascular disease within each health state. The disutility of a fracture was applied for the duration of the cycle length only for those experiencing a fracture event.

Table F4. Adverse Event-Related Disutilities

Health State	Disutility	Lower	Upper	Source
Cardiovascular Disease	-0.20	-0.11	-0.31	Sullivan et al., 2006[73]
Fracture	-0.04	-0.02	-0.06	Peasgood et al., 2009[90]

Adverse Event Costs

Long-run adverse event costs were applied to patients with risk of long-run adverse events derived from reasonable long-run assumptions used in previous analyses. Unit costs for each adverse event are stated in Table F5.

Table F5. Adverse Event Unit Costs

Long-Run Adverse Event (ICD-9-CM)	Mean ($)	Lower	Upper	Source
Fracture treatment cost (per event)	$7,093	$5,790	$8,524	Blume et al., 2011[91]
Cardiovascular disease management (per 3-months)	$1,170	$668	$1,808	Mahoney et al., 2008[92]

All costs inflated to 2018 U.S dollars.

Sensitivity Analysis Results

To demonstrate effects of uncertainty on both costs and health outcomes, we varied input parameters using available measures of parameter uncertainty (i.e. standard errors) or reasonable ranges to evaluate changes in cost per additional QALY. Inputs that had the biggest impact on ICERs include the, probability of pain recurrence (discontinuation due to lack of efficacy) for elagolix versus no active treatment, endometriosis-related pain EQ-5D score, and proportion of women on treatment (Table F6).

Table F6. One-Way Sensitivity Analyses of Elagolix versus No Active Treatment – Long-Run Time Horizon

	Lower Input Value	Upper Input Value	Lower Input Incremental Cost-Effectiveness Ratio	Upper Input Incremental Cost-Effectiveness Ratio

Pain recurrence (discontinuation due to lack of efficacy) risk ratio for elagolix vs. placebo	0.087	1.060	$75,853	$106,990
Endometriosis-related pain EQ-5D score	0.703	0.756	$71,323	$93,250
Proportion of women on treatment (elagolix)	0.827	1.000	$70,174	$82,288
Absolute difference in response to nonmenstrual pelvic pain (elagolix vs. placebo)	0.191	0.303	$87,031	$75,946
Proportion/duration of menstruation within model cycle	0.100	0.274	$84,625	$77,080
Probability of subsequent surgery	0.017	0.037	$77,265	$84,710
Mean EQ-5D for women in the United States without pain	0.916	0.924	$82,551	$79,520
Loss of fertility disutility (all subsequent hysterectomy states)	0.040	0.108	$82,314	$79,392
Absolute difference in response to dysmenorrhea pain (elagolix vs. placebo)	0.469	0.568	$82,076	$79,963
Proportion of women using add-back leuprolide post-laparoscopic surgery	0.065	0.179	$81,642	$80,187

Appendix G. Public Comments

This section includes summaries of the public comments prepared for the New England CEPAC Public Meeting on Thursday, July 12, 2018, in Burlington, Vermont. These summaries were prepared by those who delivered the public comments at the meeting and are presented in order of delivery.

A video recording of all comments can be found here, beginning at minute 01:20:30. Conflict of interest disclosures are included at the bottom of each statement for each speaker who is not employed by a pharmaceutical manufacturer.

Casey Berna, MSW
Endometriosis and Infertility Patient Advocate

We understand the benefits of birth control and NSAIDs for first line treatment of endometriosis. The side effects are well researched. When endometriosis patients are given the first line of medical treatment, they have already presented with pain and impaired quality of life. Endometriosis is already impacting their organs and vital functions. When birth control and NSAIDs no longer work, advocates want patients to be referred to multidisciplinary care, including an excision specialist, support groups, diet, and pelvic floor therapy. There is still much to learn about elagolix and side effects, but other GNRH Agonists have harmful side effects. Elagolix doesn't eradicate endometriosis nor does it cure, treat or stop the growth of the disease. The favorable things published about elagolix are researched by paid AbbVie consultants. If a drug has invasive side effects, we want it to eradicate disease and the benefits of treatment should last longer than the side effects themselves. We don't want an oral version of a drug that was harmful to so many patients. We want the drug to be studied by researchers who have no conflicts of interest. We want providers and medical organizations who decide on treatments not to be allowed to take money from drug companies. Before providers are sold on a new treatment option for patients, we first want patients referred to multidisciplinary care. We deserve better than being given a drug with noted side effects, no long term data with only the promise of temporary relief at best.

Conflicts of Interest: No conflicts to disclose

Martin Robbins, MD
New England Center for Endometriosis

My name is Dr. Martin Robbins. My practice is New England Center for Endometriosis. I specialize in Laparoscopic Excision of Endometriosis.

Endometriosis is a causative factor in up to 40% of cases of unexplained infertility. Endometriosis causes menstrual pain, painful intercourse, abdominal, pelvic, back, hip, leg pain. Endometriosis will invade the intestines and grow through the urinary tract.

Endometriosis is a surgical diagnosis. Response, or lack of response, to medication does not rule in, or rule out, Endometriosis. Endometriosis can be destroyed with laser ablation or electrical "fulguration", or endometriosis can be excised. Superficial application of laser or electrical energy does not penetrate deep enough, with persistent Endometriosis. Almost all Endometriosis centers perform excision. Excision gives the best chance for long-term pain relief, and minimizes the need for repeat surgeries.

Endometriosis and pain are still there when the patient comes off the medication. Endometriosis can remain viable in very low-estrogen environments. Endometriosis can produce its own Estrogen. Most endometriosis surgeons do not use Lupron: expensive; does not cure endometriosis; awful side effects. Estrogen-withdrawal symptoms include Osteoporosis, Depression, and impaired Memory and Concentration. Lupron and Elagolix are both antigonadotropins; Similar types of side effects can be expected.

Young women should be given oral contraceptives and anti-inflammatory medications for 3-6 months. But if pain persists, then laparoscopy is the next step. Elagolix and Lupron, should NOT be 2nd-line therapy after oral contraceptives and anti-inflammatory medications.

Elagolix and Lupron have significant side effects and are NOT harmless.

Conflicts of Interest: No conflicts to disclose

Heather Guidone, BCPA
Patient Advocate; Program Director, Center for Endometriosis Care & Executive Board Member, Endometriosis Research Center

We cannot have this discussion without acknowledging that profits have been prioritized over patients by organizations and institutions that have, for far too long, shaped the educational, treatment and funding protocols the rest of us must live with. It is no secret that the pharmaceutical industry dedicates significant resources to attempt to shape the prescribing behavior of providers, leaving patients vulnerable and susceptible to poor treatments. That system isn't broken - they built it that way…and the time has long passed to fix it. Endometriosis affects an estimated 176 million individuals globally at estimated costs into the billions. Despite its vast prevalence and substantial societal burden, it remains one of the most puzzling and challenging diseases of our time. More than just simply painful periods, 72% of patients have reported having 8 or more endometriosis-related symptoms, including but not limited to incapacitating pain apart from menstruation, infertility, painful sex, and negative impact on daily life, relationships and work

or school activities. Few conditions are more fraught by persistent inaccuracies than endometriosis, and had we been given such a seat at the table 30 plus years ago, perhaps the disease would not continue to be in the abysmal state of affairs it still is today. Like all hormone therapies for endometriosis, GnRH drugs, which have their roots in male prostate cancer and not actually women's health, are an expensive band aid – they do not improve symptoms beyond cessation of therapy nor preserve fertility. We have been here before. *[remarks continue]*

Conflicts of Interest: No conflicts to disclose

Appendix H. Conflict of Interest Disclosures

Tables G1 through G3 contain conflict of interest (COI) disclosures for all participants at the July 12, 2018 Public meeting of the New England CEPAC.

Table H1. ICER Staff and Consultant COI Disclosures

Name	Organization	Disclosures
Dan Ollendorf, PhD	ICER	None
Steven J. Atlas, MD, MPH	Massachusetts General Hospital	None
R. Brett McQueen, PhD	University of Colorado Anschutz Medical Campus	None

Table H2. New England CEPAC Panel Member COI Disclosures

Name	Organization	Disclosures
Robert H. Aseltine Jr., PhD	UCONN Health	*
Teresa Fama, MD	Central Vermont Medical Center	*
Christopher Jones, PhD	Assistant Professor of Surgery and Assistant Professor of Economics; University of Vermont College of Medicine	*
Claudio W. Gualtieri, JD	AARP	*
Claudia B. Gruss, MD, FACP, FACG, CNSC	Western Connecticut Medical Group	*
Stephen Kogut, PhD, MBA, RPh	University of Rhode Island College of Pharmacy	*
Stephanie Nichols, PharmD, BCPS, BCPP	Husson University; Maine Medical Center	*
Brian P. O'Sullivan, MD	Dartmouth College	*
Jeanne Ryer, MSc, EdD	New Hampshire Citizens Health Initiative	*
Jason Wasfy, MD, MPhil	Massachusetts General Hospital	*
Rev. Albert Whitaker, MA	American Diabetes Association	*

* 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.

Table H3. Policy Roundtable Disclosures

Name	Organization	Disclosures
Casey Berna, MSW	Endometriosis and Infertility Patient Advocate	No conflicts to declare
William Brewster, MD, FACP, CHIE	Vice President; Harvard Pilgrim Health Care, New Hampshire Market	Employee of Harvard Pilgrim Health Care
Rebecca Flyckt, MD	Director, Fertility Preservation Program, Obstetrics, Gynecology and Women's Health Institute Cleveland Clinic	No conflicts to declare
Heather Guidone, BCPA	Patient Advocate; Program Director, Center for Endometriosis Care; Executive Board Member Endometriosis Research Center	No conflicts to declare
Nancy Hogue, PharmD	Director of Pharmacy Services Department of Vermont Health Access	Employee of Vermont state Medicaid
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	My office is under consideration for a site on one of ABBVIE clinical trials. I have participated in a variety of clinical trials over the years and it does not affect my evaluation of drug effectiveness as a clinical scientist, nor my use of it as a provider which depends on a medications cost effectiveness.