Elagolix for Endometriosis: Effectiveness and Value

Background and Scope

February 9, 2018

Background

Endometriosis is a chronic gynecological condition characterized by the attachment and proliferation of endometrial cells outside of the uterus.[1] It affects 6-10% of women of reproductive age, with peak prevalence between 25 to 35 years of age.[2,3] 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.[4,5] It can also affect ability to work,[6] 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 is a cause of pelvic pain in up to 60% of teenage girls and women, and 50% of women with infertility.[3] A number of other conditions of the reproductive tract can cause pelvic pain as well as other non-gynecological disorders. Physical examination findings, blood tests and non-invasive imaging can help exclude other causes of pelvic pain, but are not accurate enough to establish a definitive diagnosis of endometriosis in most cases.[9] As such, the diagnosis of endometriosis is often delayed in women and contributes to the burden of pain, infertility, and quality of life.[4] Direct visualization at surgery is the definitive way to diagnose and stage endometriosis, but the extent of disease observed often does not correlate with the intensity or character of reported pain.[10] Nevertheless, empirical therapy is often initiated without surgery after other conditions are excluded, but without a definitive diagnosis of endometriosis. In addition to direct visualization at the time of surgery, removal of implants (endometrial lesions found in the ovaries, Fallopian tubes, or the peritoneum) provides pathological confirmation and symptom relief.

Treatment recommendations have been developed by the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine.[11,12] A range of pharmacologic and surgical treatments are available and have been shown to decrease patient symptoms. Initial treatment includes a trial of nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal therapy, typically combined with oral contraceptives (OCPs).[13] In addition to OCPs, progestins are used and can be administered orally, or via depot injections, implants or levonorgestrel-releasing intrauterine

devices (IUDs). All hormonal therapies studied (OCPs, progestins and gonadotropin-releasing hormone [GnRH] agonists) have shown similar benefits, but have major differences in side effects and costs, and only some are FDA-approved specifically for endometriosis.[14] In addition, GnRH agonists are not considered first-line therapy and are not recommended for adolescents because of concerns about long-term bone loss. If a GnRH agonist is used, estrogen-progestin add-back therapy is commonly recommended.[15] In addition to GnRH agonists and certain progestins, danazol is also FDA-approved for treatment of endometriosis but is rarely used in clinical practice for this indication. Finally, aromatase inhibitors, which are approved for breast cancer in women and gynecomastia in men, have been used off-label to treat endometriosis.

Surgery can be a first-line therapy, often at the time of a diagnostic laparoscopy, or initiated after an insufficient response to medical therapy.[16,17] Hormonal therapy after surgery may prolong treatment benefit in some patients, especially those with more severe symptoms and findings. Though women with endometriosis have higher rates of infertility, pregnancy often results in decreased symptoms, and symptoms typically disappear permanently with the onset of menopause.[18] For those with moderate or severe symptoms, pain management may require repeated courses of hormonal or surgical treatments until menopause,[19] and chronic pain due to endometriosis is a cause of chronic opioid use with its attendant risks.[20] Definitive therapy with removal of the uterus and ovaries (hysterectomy and bilateral salpingo-oophorectomy) is reserved for women with symptoms that are not controlled with other treatments and who have completed childbearing.

There are currently three GnRH agonists approved by the FDA for the treatment of pelvic pain caused by endometriosis: leuprolide (Eligard®, Tolmar Pharmaceuticals; Lupron Depot®, AbbVie), nafarelin (Synarel®, Pfizer), and goserelin (Zoladex®, TerSera Therapeutics/AstraZeneca). These agents have been in clinical use for over 25 years and have well described limitations. First, during the first 10-14 days of treatment with these agents, binding to the GnRH receptor stimulates the pituitary gland to release hormones (luteinizing hormone [LH] and follicle stimulating hormone [FSH]) that will increase symptoms. This necessitates the use of a OCP or a progestin, commonly norethindrone, at the same time to prevent worsening symptoms. 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 lead to suppression of production of estradiol and progesterone by the ovaries. The low estrogen state induced by GnRH agonists lead to the main side effects including hot flashes, vaginal dryness, decreased libido, mood swing and headache. In addition, prolonged use of GnRH agonists can lead to decreased bone density (osteoporosis). Therefore, these medicines are approved for only up to six months of continuous use. The use of add-back hormonal therapy is commonly given to decrease symptoms and can permit longer-term use.

Given these limitations, 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 (investigational, AbbVie), is under FDA review for patients with endometriosis. It is a GnRH antagonist, and unlike GnRH agonists, it does not cause an initial surge in LH and FSH, suppresses ovarian hormone levels immediately rather than taking 7-14 days, and the degree of ovarian suppression is dose dependent. Moreover, it is an oral medication, unlike GnRH agonists that are given by injection or intranasally.

As such, ICER has decided to focus attention on endometriosis for this review and consider the role of the GnRH antagonist elagolix. In addition to the above stakeholder groups, input was solicited directly from the manufacturer of elagolix during a 3-week public comment period. ICER looks forward to continued engagement with these stakeholders throughout the entire project timeline, up to and including the public meeting in July 2018.

Stakeholder Input

This scoping document was developed with input from patient advocacy organizations and clinicians. These groups suggested that symptoms of endometriosis are impactful on quality of life, both physically and emotionally, and helped to inform the research direction outlined in this revised scope. Stakeholders indicated that endometriosis can be a serious and disabling condition that affects women throughout their reproductive years. Despite being a common cause of chronic pelvic pain, its diagnosis is often delayed. Initial treatment primarily focuses on the use of NSAIDs and hormonal contraceptives, either combined oral contraceptives or progestin-only medications. For women whose symptoms are not adequately controlled, laparoscopy to establish a definitive diagnosis prior to further treatment or a trial of a GnRH agonist is considered.

Report Aim

This project will evaluate the health and economic outcomes of elagolix for endometriosis. The ICER value framework includes both quantitative and qualitative comparisons across treatments to ensure that the full range of benefits and harms - including those not typically captured in the clinical evidence such as innovation, public health effects, reduction in disparities, and unmet medical needs - are considered in the judgments about the clinical and economic value of the interventions.

Scope of the Clinical Evidence Review

The proposed scope for this assessment is described on the following pages using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence will be abstracted from randomized controlled trials as well as high-quality systematic reviews; high-quality comparative cohort studies will be considered, particularly for long-term outcomes and

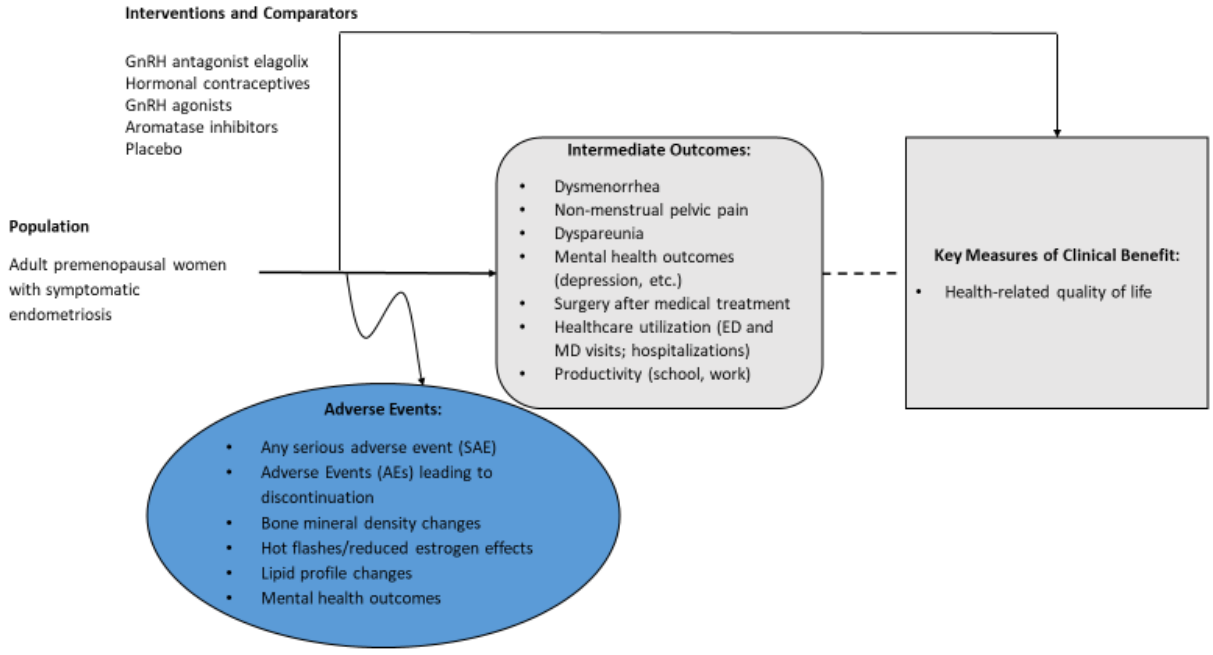
uncommon adverse events. Our evidence review will include input from patients and patient advocacy organizations, data from regulatory documents, information submitted by manufacturers, and other grey literature when the evidence meets ICER standards (for more information, see https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/grey-literature-policy/).

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

Analytic Framework

The general analytic framework for assessment of therapies for endometriosis is depicted in Figure 1.1 on the following page.

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 non-menstrual 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.[21]

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. Intervention(s) of interest were developed with input from patient organizations, clinicians, manufacturers, and payers on which drugs to include.

Comparators

Data permitting, we intend to compare elagolix to GnRH agonists (with or without low- dose hormone replacement), hormonal contraceptives, aromatase inhibitors, and placebo.

Outcomes

This review will examine key clinical outcomes associated with endometriosis. The anticipated outcomes of interest and key harms are described in the table below. We will engage with patient groups and clinical experts to ascertain which outcomes are of greatest importance to patients and seek patient-reported outcomes or other evidence sources to enrich the available data. Initial discussion with patients, patient groups, and clinicians indicate 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 will include:

Table 1.2. Key Outcomes and Harms

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

Evidence tables will be developed for each selected study and results will be summarized in a qualitative fashion; if feasible, random- or fixed-effects meta-analysis will be used to quantitatively summarize outcomes for the therapies of interest. In addition, we will consider network meta-analysis to combine direct and indirect evidence of effectiveness if available data permit.

Timing

Evidence on intervention effectiveness and harms will be derived from studies of at least three months duration.

Settings

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

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 table below.

Table 1.1. Potential Other Benefits and Contextual Considerations

Potential Other Benefits
This intervention provides significant direct patient health benefits that are not adequately captured by the QALY.
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 who have failed other available treatments.
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.
Potential 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 comparator," there is significant uncertainty about the long-term risk of serious side effects of this intervention.
Compared to "the comparator," 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.

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

Comparative Value Analyses

As a complement to the evidence review, we will develop a decision-analytic model to assess the cost-effectiveness of elagolix relative to relevant comparator treatments (e.g., hormonal contraceptives, GnRH agonists, aromatase inhibitors, placebo) in the management of endometriosis with associated pain. The model will be evaluated from a health-system perspective. The primary population of interest will be adult premenopausal women with symptomatic endometriosis.

The decision analytic model structure will be informed by previous modeling evidence, Phase III clinical trials for elagolix, and stakeholder input. The model will include a short-term decision tree and a long-term Markov model to evaluate the cost-effectiveness of elagolix as compared to relevant comparators for the management of pain associated with endometriosis. The decision tree will calculate the costs and consequences of six months of treatment with elagolix, including

pathways relevant to short-term outcomes, such as response to treatment (e.g. pain reduction).[22] Six months, as a time horizon, was determined to be suitable due to its relationship with trial duration and previous modeling analyses.[23] Given available evidence, longer-term outcomes[24] will be assessed via a Markov model. Patients will transition between endometriosis pain-related health states during three-month cycles (in keeping with the typical interval for pain measurement in clinical trials) over a model time horizon that ends at menopause onset. The Markov model will be flexibly defined to include on- and off-treatment health states, to allow for events such as suspension of treatment to attempt pregnancy. Adverse clinical events from long-term use of elagolix and comparator agents will be included as weighted adverse event costs, as informed by clinical trial evidence on the proportion of women developing serious adverse events.

Key model inputs will include response and recurrence rates, quality of life values, occurrence of adverse events, costs of treatment, surgery, and other endometriosis-related health care services, as well as mortality. Probabilities, costs, and other inputs will differ between treatments to reflect varying effectiveness between interventions; however, health state utility values will be consistent across interventions.

Each intervention will be evaluated in terms of the proportion with clinical response (with respect to dysmenorrhea and non-menstrual pelvic pain) at six months. With available evidence, health outcomes of life years and quality-adjusted life years (QALYs) gained will also be evaluated. In order to estimate life years and cost per life year gained, evidence will be required by intervention including health state transition probabilities and costs within each health state. In order to estimate QALYs, quality of life weights will be obtained for each health state, including quality of life decrements for adverse events. Given available evidence, the cost per responder, incremental cost per life year gained, and incremental cost per QALY gained will be calculated.

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

More information on ICER's methods for estimating potential budget impact can be found at: http://icer-review.org/wp-content/uploads/2016/02/ICER-Value-Assessment-Proposed-Updates-Webinar-021317.pdf.

Identification of Low-Value Services

As described in its Final Value Assessment Framework for 2017-2019, ICER will now include in its reports information on wasteful or lower-value services in the same clinical area that could be reduced or eliminated to create additional resources in health care budgets for higher-value innovative services (for more information, see https://icer-review.org/material/final-vaf-2017-2019/). These services are ones that would not be directly affected by elagolix as these services will be captured in the economic model. Rather, we are seeking services used in the current management of endometriosis beyond the potential offsets that arise from a new intervention. ICER encourages all stakeholders to suggest services (including treatments and mechanisms of care) that could be reduced, eliminated, or made more efficient.

References

1. Giudice LC. Endometriosis. *N Engl J Med.* 2010;362:2389-2398.
2. Missmer Stacey A, Hankinson Susan E, Spiegelman Donna, Barvieri Robert L, Marshall Lynn M, Hunter David J. Incidence of Laparoscopically Confirmed Endometriosis by Demographic, Anthropometric, and Lifestyle Factors. *American Journal of Epidemiology.* 2004;160(8).
3. Eskenazi B, Warner ML. EPIDEMIOLOGY OF ENDOMETRIOSIS. *Obstetrics and Gynecology Clinics.* 1997;24(2):235-258.
4. Nnoaham KE1, Hummelshoj L, Webster P, et al. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. 2011.
5. Vercellini P, Meana M, Hummelshoj L, Somigliana E, Viganò P, L F. Priorities for Endometriosis Research: A Proposed Focus on Deep Dyspareunia. *Reprod Sci.* 2011.
6. Soliman AM, Coyne KS, Gries KS, Castelli-Haley J, Snabes MC, Surrey ES. The Effect of Endometriosis Symptoms on Absenteeism and Presenteeism in the Workplace and at Home. *Journal of managed care & specialty pharmacy.* 2017;23(7):745-754.
7. Soliman AM, Yang H, Du EX, Kelley C, Winkel C. The direct and indirect costs associated with endometriosis: a systematic literature review. *Hum Reprod.* 2014;31.
8. Simoens S, Dunselman G, Dirksen C HL, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod.* 2012.
9. Nisenblat V, Prentice L, Bossuyt PMM, Farquhar C, Hull ML, N J. Combination of the non-invasive tests for the diagnosis of endometriosis. *Cochrane Database of Systematic Rev.* 2016.
10. Vercellini P, Trespidi L, De Giorgi O, Cortesi I, Parazzini F, PG C. Endometriosis and pelvic pain: relation to disease stage and localization. *Fertil Steril.* 1996;65(2):299-304.
11. ACOG. Practice bulletin no. 114: management of endometriosis. *Obstet Gynecol.* 2010.
12. ASRM. Treatment of pelvic pain associated with endometriosis. *American Society for Reproductive Medicine.* 2014;101(4):927-935.
13. Brown J, Crawford TJ, Allen C, Hopewell S, Prentice A. Nonsteroidal anti-inflammatory drugs for pain in women with endometriosis. *Cochrane Database Syst Rev.* 2017;1:Cd004753.
14. Brown J, Pan A, RJ H. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis (Review. *Cochrane Database Syst Rev.* 2010.
15. Wu D, Hu M, Hong L, et al. Clinical efficacy of add-back therapy in treatment of endometriosis: a meta-analysis. *Archives of gynecology and obstetrics.* 2014;290(3):513-523.
16. Chaichian S, Kabir A, Mehdizadehkashi A, Rahmani K, Moghimi M, Moazzami B. Comparing the Efficacy of Surgery and Medical Therapy for Pain Management in Endometriosis: A Systematic Review and Meta-analysis. *Pain Physician.* 2017;20(3):185-195.
17. Duffy JMN, Arambage K, Correa FJS, et al. Laparoscopic surgery for endometriosis (Review). *Cochrane Database Syst Rev.* 2014.
18. Gemmell LC, Webster KE, Kirtley S, Vincent K, Zondervan KT, Becker CM. The management of menopause in women with a history of endometriosis: a systematic review. *Human reproduction update.* 2017;23(4):481-500.
19. Ofer A, Shulman LP, SS. S. Improving the Treatment and Management of Endometriosis: An Overview of Current and Novel Approaches. *Am J Obstet Gynecol.* 2016.
20. Steele A. Opioid use and depression in chronic pelvic pain. *Obstetrics and gynecology clinics of North America.* 2014;41(3):491-501.
21. Woolf S. *An organized analytic framework for practice guideline development: using the analytic logic as a guide for reviewing evidence, developing recommendations, and explaining the rationale.*: Agency for Health Care Policy and Research;1994.

22. Sanghera S, Barton P, Bhattacharya S, Horne AW, Roberts TE. Pharmaceutical treatments to prevent recurrence of endometriosis following surgery: a model-based economic evaluation. *BMJ open.* 2016;6(4):e010580.
23. Taylor HS, Giudice LC, Lessey BA, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *N Engl J Med.* 2017;377(1):28-40.
24. Wu B, Yang Z, Tobe RG, Wang Y. Medical therapy for preventing recurrent endometriosis after conservative surgery: a cost-effectiveness analysis. *BJOG : an international journal of obstetrics and gynaecology.* 2017.