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New Drug Evaluation: Elagolix tablet, oral

Date of Review: November 2018
Generic Name: elagolix sodium

End Date of Literature Search: September 2018
Brand Name (Manufacturer): Orilissa™ (AbbVie, Inc)
Dossier Received: yes

Research Questions:

1. What is the efficacy of elagolix compared to placebo or currently available therapy for the treatment of moderate to severe pain associated in women with endometriosis?
2. Is elagolix safe for the treatment of moderate to severe pain associated in women with endometriosis?
3. Are there any subgroups (based on age, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with elagolix?

Conclusions:

- There is moderate quality evidence from two phase 3 studies that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant difference in dysmenorrhea symptoms as measured by the Endometriosis Daily Pain Impact Diary (EDPID) score at 3 months when treated with elagolix 150 mg daily and 200 mg twice daily versus placebo (absolute risk reduction [ARR]=27%/number needed to treat [NNT]=4 and ARR=56%/NNT=2, respectively for Elaris EM-1; ARR=21%/NNT=5 and ARR=50%/NNT=2, respectively for Elaris EM-2).[1,2,3] The clinical significance of this difference is unclear.
- There is moderate quality evidence from two phase 3 studies that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant difference in non-menstrual pelvic pain symptoms as measured by the EDPID score at 3 months when treated with elagolix 150 mg daily and 200 mg twice daily versus placebo (ARR=14%/NNT=8 and ARR=18%/NNT=6, respectively for Elaris EM-1; ARR=13%/NNT=8 and ARR=21%/NNT=5, respectively for Elaris EM-2). [1,2,3] The clinical significance of this difference is unclear.
- There is moderate quality evidence from two phase 3 studies that a higher proportion of adult women with endometriosis-related pain experienced a statistically significant reduction in dyspareunia symptoms as measured by a decreased dyspareunia pain score (5-point scale, from 0 to 4) at 3 months when treated with elagolix 200 mg twice daily versus placebo (-0.49 vs -0.20, respectively; $p<0.001$ for Elaris EM-1; -0.60 vs -0.30, respectively; $p<0.001$ for Elaris EM-2). [1,2,3] The clinical significance of this difference is unclear.
- There is insufficient evidence to evaluate the long-term safety of elagolix. The safety population included 1686 patients. Serious adverse events were similar compared to placebo. Adverse events more common with either elagolix 150mg daily or 200mg twice daily versus placebo included hot flush (elagolix 150 mg daily, 10%; elagolix 200 mg BID, 16%; placebo, 13%) and headache (elagolix 150 mg daily, 17%; elagolix 200 mg BID, 20%; placebo, 12%).[1,2,3]

- There is insufficient evidence to compare the safety and efficacy of elagolix to any other analgesics, oral contraceptives, gonadotropin-releasing hormone (GnRH) analogs, danazol, or progestins for treatment of endometriosis-related pain in specific subpopulations.

Recommendations:
- Create a new preferred drug list (PDL) class for gonadotropin-releasing hormone (GnRH) receptor antagonists.
- Implement prior authorization criteria for elagolix (**Appendix 2**).

Background:
Endometriosis is a gynecological inflammatory condition commonly associated with chronic pain and infertility caused by the growth of estrogen-dependent endometrial-like tissue implanted outside of the uterine cavity.[4] In 2017, the prevalence of endometriosis in the United States was estimated to be roughly 5 million people.[5] It is estimated that 1 in 10 women between the ages of 15-49 may experience endometriosis with the highest incidence among those between 25 and 29 years of age.[5] Quality of life and work productivity are negatively impacted by endometriosis pain.[6] In the United States alone, it is estimated that endometriosis results in over $10,000 in additional health care costs as well as $15,000 in lost productivity per patient year.[7] Epidemiologic studies have concluded that women with early menarche (<10 years old) with more frequent menstrual cycles (<28 days) and longer menstrual flows (>5-6 days) are at higher risk for endometriosis.[5] There are more than 1500 women currently in Oregon Medicaid Fee-for-Service (FFS) with claims indicative of an endometriosis-related diagnosis between July 2016 and June 2017.

As the most common cause of unexplained pelvic pain, endometriosis may be suspected through ultrasound and confirmed by histologic confirmation of lesions through laparoscopy.[8] Ectopic lesions occur most commonly around the ovaries but may also be found elsewhere in the body including the uterosacral ligaments, uterovesical peritonium, and other pelvic and even non-pelvic area locations.[9,10] During menstruation, the endometriotic tissue responds to hormonal stimulation similarly to the endometrium itself with associated bleeding and inflammation.[11] Over time, the inflammation leads to fibrosis and adhesions which may result in pelvic anatomical changes that range from symptoms of slight discomfort to severe disabling pelvic pain and dyspareunia.[11] The type, duration, and magnitude of pain may vary greatly among individuals and often manifests independently of the menstrual cycle.[7] Up to 50% of women with endometriosis become infertile.[5] It is not uncommon for endometriosis patients to experience depression and other mental health issues because of their condition.[7]

Endometriosis treatment varies based on duration and severity of symptoms. Surgery is an option in women with endometriosis who do not respond to medical therapy, especially for those with plans to become pregnant.[9,12] Due to the response of ectopic endometrial tissue to ovarian hormones, efforts to produce a hypoestrogenic state form the basis of therapeutic approaches to endometriosis symptom management.[9,12] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[9,12] Therefore, most women are given a steady administration of combined hormonal contraceptives, or progestin alone, for first-line treatment of endometriosis pain.[6,9] Hormonal therapies such as gonadotropin-releasing hormone (GnRH) agonists have also been used for management of endometriosis.[6,9] Continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[9,12] Goserelin, leuprolide, and nafarelin are all FDA-approved for endometriosis therapy.[2] Danazol, a gonadotropin inhibitor, was the first FDA-approved agent for endometriosis, but its utility has been undermined by a significant adverse effect profile.[2,9] Another group of estrogen biosynthesis blockers under investigation are the aromatase inhibitors which are currently used off-label for endometriosis treatment.[9] FDA-approved agents for the management of endometriosis are listed in **Table 1**.

Table 1. Summary of FDA-approved Therapies for Endometriosis (modified)[2]

Drug	Dosing/Administration	Select Safety Precautions
Danazol	200 to 400 mg orally given in 2 divided doses; adjust depending on clinical response; OR 800 mg orally in 2 divided doses; titrate downward depending on clinical response	-Thrombotic events including strokes -Peliosis hepatis and benign hepatic adenoma -Intracranial hypertension -Lipoprotein changes -Androgen effects -Use in pregnancy is contraindicated
Goserelin acetate	3.6 mg implant subcutaneously placed every 28 days for 6 months maximum	-Hyperglycemia and increased risk of developing diabetes -Loss of bone mineral density (BMD) -Hypoestrogenism -Serum lipid changes -Use in pregnancy is contraindicated
Leuprolide acetate (monthly depot and 3-month depot)	3.75 mg IM depot injection monthly for 6 months OR Initial, 11.25 mg IM depot injection once every 3 months for 1 or 2 doses (maximum 6 months)	-Loss of BMD -Worsening depression and memory disorders -Convulsions -Breakthrough bleeding/risk of pregnancy
Nafarelin acetate	400 mcg/day INTRANASALLY by 1 spray (200 mcg) into 1 nostril in the morning and 1 spray (200 mcg) into the other nostril in the evening; MAX 800 mcg/day; initiate treatment between days 2 and 4 of the menstrual cycle; recommended duration 6 months	-Loss of BMD -Worsening depression -Hypoestrogenism -Serum lipid changes
Medroxyprogesterone acetate	1 injection (104 mg per 0.65 mL) subcutaneously into the anterior thigh or abdomen once every 3 months (12 to 14 weeks); do not use for longer than 2 years	-Loss of BMD -Thromboembolic disorders -Breast cancer risk -Ocular disorders -Ectopic pregnancy -Bleeding irregularities
Leuprolide acetate + norethindrone acetate	See leuprolide acetate dosing above plus 5 mg norethindrone acetate orally daily	-Loss of BMD -Recurrence of depression -Convulsions

The National Institute for Health and Care Excellence (NICE) has recently updated guidance documents for management of endometriosis with various treatments including diagnostic recommendations, pharmacotherapy options for pain, and surgery.[13] It is recommended that endometriosis be diagnosed through abdominal and pelvic examination, magnetic resonance imaging (MRI) or ultrasound, and diagnostic laparoscopy with biopsy when needed.[13] NICE recommends that pain from endometriosis be treated with a short trial of NSAIDs and/or acetaminophen, then an oral contraceptive or progestin.[13] Surgical

excision is recommended for women with suspected or confirmed endometriosis with bowel, bladder, or ureter involvement.[13] GnRH agonists may be considered as adjunct treatment prior to surgery for deep endometriosis.[13] NICE recommends a hysterectomy with or without oophorectomy for women with endometriotic complications unresponsive to other treatments.[13]

There are several non-specific assessment scales that have been used to measure patient response to medical treatment intervention. The Patient Global Impression of Change (PGIC) is a general tool used to evaluate the overall health status as perceived by the patient using a seven-point single-item scale ranging from 'very much worse' to 'very much improved'.[14] The PCIG has been applied as a valid tool in many clinical trials of analgesics but it lacks ability to reflect degrees of change within specific domains.[14] For pain assessment, the visual analogue or verbal rating scale is a numeric rating scale which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable).[15] The ease of administration and scoring allows this tool to be used in a variety of settings, however, it may not be appropriate for low literacy patients.[15] A similar pain assessment tool commonly used is the Brief Pain Inventory (BPI) which has the added benefit of assessing both pain severity and interference it has on various aspects of daily activities.[16] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[16] A specific tool known as the Biberoglu and Behrman (B&B) Scale is patient-reported symptom assessment tool for dysmenorrhea, chronic pelvic pain, dyspareunia, as well as pelvic tenderness and induration.[16] The B&B is graded on a scale from 0 to 3 (or 4 for dyspareunia) with higher scores representative of more symptoms.[16] However, several organizations including the National Institutes of Health have indicated that the B&B has never been validated nor administered consistently.[16] Quality of Life (QoL) assessment tools such as the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and the European Quality of Life in 5 Dimensions (EQ-5D) have been developed for use in many medical conditions, but there has not been a strong correlation found between QoL and pain intensity with use of these scales in endometriosis patients.[16] The Endometriosis Health Profile (EHP) is a disease-specific instrument used to assess the quality of life in women with endometriosis.[16] The EHP-5 is a shorter version of the EHP-30.[16] Both explore the same five core dimensions including pain, control and powerlessness, emotional well-being, social support, and self-image.[16] The EHP-30 has been validated for use in women with endometriosis, while the EHP-5 has not.[16]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Elagolix is an oral, nonpeptide, gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis.[2,3] GnRH antagonists are thought to reduce gonadotropin secretion from the pituitary gland in a dose dependent manner to decrease estradiol and progesterone concentrations.[17] In women with endometriosis, a reduction in estrogen may limit the growth of endometriotic tissue which is the source of localized pain and inflammation characteristic of the condition.[17] The FDA approval of elagolix for the treatment of women with endometriosis pain was based on two pivotal trials which are described and evaluated below in **Table 4**.[2,3]

Elaris Endometriosis 1 and 2 (EM-1 and EM-2) were virtually identical phase 3, randomized, double blind studies designed to evaluate the effectiveness of two different doses of elagolix versus placebo in the treatment of women with moderate to severe endometriosis-associated pain.[1,2] EM-1 (N=872) took place in the United States and Canada, while EM-2 (N=817) enrolled patients from U.S., Europe, South America, Australia, New Zealand, and South Africa.[1,2] Baseline demographics, inclusion criteria, and exclusion criteria are reported in **Table 4**.[1,2] After a washout period, patients were screened for up to 100 days with assessment of baseline pain scores to verify moderate to severe endometriosis-associated pain.[1,2] Study subjects were switched from their usual analgesic to an

approved rescue analgesic of naproxen and/or a select opioid followed by a 6-month treatment period.[1,2] Eligible patients were randomized in a 2:2:3 ratio to receive oral elagolix 150 mg tablet once daily (low dose), 200 mg twice daily (high dose), or placebo.[1,2]

The co-primary endpoints for efficacy in Elaris EM-1 and Elaris EM-2 were the proportion of women with dysmenorrhea and proportion of women with non-menstrual pelvic pain who responded to treatment based on the mean results of a patient-reported Endometriosis Daily Pain Impact Diary (EDPID) at month 3.[1,2] The EDPID was a modified version of the B&B Scale assessment tool created to assess endometriosis symptom severity.[1,2] Four questions regarding dysmenorrhea, non-menstrual pelvic pain, and dyspareunia were graded on a 3-point pain score scale: 0/1=no/mild, 2=moderate, 3=severe (total score range of 0-12).[1,2] For each of the co-primary endpoints, a logistic regression model was used to analyze the data.[1,2] A subject was considered a responder if the reduction of pain at month 3 compared to baseline met or exceeded the calculated minimal clinically important difference (MCID) as determined by a receiver operating characteristics (ROC) analysis.[1,2] The ROC analysis used last observation carried forward for missing data on subjects who prematurely discontinued the study before month 3.[1,2] The authors reported that the clinically meaningful threshold for mean change from baseline was -0.81 for Elaris EM-1 and -0.85 for Elaris EM-2 compared to placebo for dysmenorrhea symptoms.[1,2] For non-menstrual pelvic pain, the authors reported that the patient responder threshold was a minimum improvement of -0.36 for Elaris EM-1 and -0.43 for Elaris EM-2 compared to placebo.[1,2] The PGIC scale was also co-administered monthly to assess secondary endpoints and to serve as an anchor for the ROC analysis.[1,2] Results for each co-primary endpoint at week 6 were also analyzed.[1,2] Dyspareunia, a key secondary endpoint, was assessed by patient response to a daily 5-question, 3-point pain rating scale, which was averaged monthly.[1,2] The ROC MCID threshold for dyspareunia was estimated to be -0.29 (-35.1%).[1,2]

In both trials, statistically significant reductions in dysmenorrhea pain were reported by roughly 44% of the low-dose elagolix group, 74% of the high-dose elagolix group, and 21% of the placebo group (P<0.001).[1,2] Non-menstrual pelvic pain was also reported to decrease in treatment groups, with roughly 50% of low dose, 56% of high dose, and 36% of placebo groups demonstrating a statistically significant benefit (P<0.001).[1,2] See **Table 4** for percentages from each individual trial. For dyspareunia, only the 200 mg twice daily high-dose elagolix reported a statistically significant drop in pain rating score versus placebo for Elaris EM-1 (-0.49 vs. -0.20, respectively; p<0.001) and Elaris EM-2 (-0.60 vs. -0.30, respectively; p<0.001).[1,2] The clinical significance of a -0.2 to -0.3 change on a dyspareunia pain assessment scale that ranges from 0 to 3 is unclear.

Limitations

Details of the ROC analysis and development of the statistical prediction models used to map the author's calculations to clinical outcome thresholds were not reported. Use of the PGIC scale has not been established as a well-defined and reliable measure of endometriosis-associated pain. Neither the EDPID nor the B&B symptom scale has been validated as an assessment tool for endometriosis pain measurements. However, the authors used their PGIC data from the trial as an anchor to establish the MCID on the EDPID. Use of an unvalidated tool with no clear MCID threshold in endometriosis assessment presents a major challenge for the determination of true patient response and the clinical usefulness of the reported findings.

Clinical Safety:

The safety of elagolix was evaluated in women who completed the six months of treatment and met eligibility criteria for continued treatment in two uncontrolled, blinded six-month extension trials, Elaris EM-3 and Elaris EM-4, for a total treatment duration of up to 12 months.[1,2,3] The most common serious adverse events reported for elagolix subjects in Elaris EM-1 (N=475) and Elaris EM-2 (N=477) included appendicitis (0.3%), abdominal pain (0.2%), and back pain (0.2%).[1,2,3] In these trials, 0.2% of subjects treated with elagolix 150 mg once daily and 0.2% of subjects treated with elagolix 200 mg twice daily discontinued therapy due to serious adverse reactions compared to 0.5% of those given placebo.[1,2,3] For the two trials, the study discontinuation rates due to adverse reactions for low dose elagolix, high-dose elagolix, and placebo were 5.5%, 9.6%, and 6.0% respectively. [1,2,3] The most common treatment-emergent adverse

events which lead to study discontinuation for low dose and high dose elagolix were hot flushes/night sweats (1.1% and 2.5% respectively), and nausea (0.8% and 1.5%, respectively). Adverse events appeared to be dose-related.[1,2,3] Most discontinuations due to hot flushes or night sweats (10 of 17, 59%) and nausea (7 of 11, 64%) occurred within the first 2 months of therapy.[1,2,3] In the long-term phase 3 analysis which included studies Elaris EM-3 and Elaris EM-4, there were several discontinuations in the high dose elagolix group due to decreased BMD (3.6%) compared to low-dose (0.3%).[1,2,3] Common adverse reactions reported in 5% or more women in the low and high-dose elagolix treatment groups versus placebo were hot flush or night sweats, headache, nausea, mood swings, amenorrhea, depressive symptoms, anxiety, and arthralgia which are summarized below in **Table 2**. [1,2,3]

Table 2. Percentage of Subjects in Studies EM-1 and EM-2 with Treatment-Emergent Adverse Reactions in ≥5% of Subjects and ≥2% than Placebo [2,3]

	Elagolix 150 mg Once Daily; % N=475	Elagolix 200 mg Twice Daily; % N=477	Placebo; % N=734
Hot flush or night sweats	24	46	9
Headache	17	20	12
Nausea	11	16	13
Insomnia	6	9	3
Altered mood swings	6	5	3
Amenorrhea	4	7	<1
Depressed mood	3	6	2
Anxiety	3	5	3
Arthralgia	3	5	3

Severe adverse events with elagolix treatment included bone loss in both the higher dose (7%) and lower dose (2%) compared to placebo (<1%).[2,3] Other serious adverse events with elagolix therapy included suicidal ideation and mood disorders, hepatic transaminase elevations, and potential for reduced efficacy with estrogen-containing contraceptives. These occurred at a higher than placebo but still roughly 1% or less overall.[2,3]

For women with moderate hepatic impairment (Child-Pugh B), elagolix 150 mg once daily should be the maximum dose not to be used for more than 6 months.[3] Elagolix is contraindicated in women with severe hepatic impairment (Child-Pugh C), in women who are pregnant, have known osteoporosis, or are taking any strong organic anion transporting polypeptide (OATP) 1B1 Inhibitors.[3]

The FDA labeling limited the use of elagolix to a 6-month treatment period due to concerns of dose-dependent bone loss.[2,3] Both studies combined revealed a decline in BMD of greater than 8% at any anatomic site in 2 (0.4%) placebo subjects, 5 (1%) in the elagolix 150 mg once daily arm and 24 (6%) in the elagolix 200 mg BID arm. [2,3] The extension studies demonstrated 12 (5%) additional patients on elagolix 150 mg once daily and 51 (21%) additional patients in the elagolix 200 mg BID group had bone loss of greater than 8% at any site compared to pre-treatment baseline. [2,3] Elagolix treatment was also associated with greater incidence of depressive symptoms in both elagolix 200 mg and 150mg groups versus placebo (6% and 3% vs. 2%, respectively).[2,3]

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Pain relief
2) Health-related quality of life
3) Serious adverse events
4) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Proportion of women with clinical response to dysmenorrhea as measured by the EDPID score at 3 months
2) Proportion of women with clinical response to non-menstrual pelvic pain as measured by the EDPID score at 3 months

Table 3. Pharmacology and Pharmacokinetic Properties. [2,3]

Parameter	
Mechanism of Action	GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland which results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone.
Oral Bioavailability	~50%
Distribution and Protein Binding	80%; to human plasma proteins
Elimination	Hepatic metabolism
Half-Life	4-6 hours
Metabolism	CYP3A (major); Minor pathways include: CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs)

Abbreviations: GnRH = gonadotropin releasing hormone; CYP = cytochrome P

Table 4. Comparative Evidence Table.[1,2]

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
Taylor, et al (Study M12-665; Elaris EM-1) Phase 3 RCT, DB, PC study of patients with endometriosis	1. Placebo orally twice daily 2. Elagolix 150 mg orally once daily and oral placebo once daily	Demographics: -Mean age: 32 years -Race: -White: 87% -Black: 9% -Other: 4% -Mean BMI (kg/m^2): 28 -Analgesic Use (NSAID, Opioid, or both): >90% Key Inclusion Criteria:	ITT: 1. 374 2. 249 3. 248 PP: 1. 274 2. 195 3. 183 Attrition: 1. 27% 2. 22%	Primary Endpoints: Proportion of women with a clinical response to dysmenorrhea as measured by the EDPID score at 3-months: 1. 73/373 (19.6%) 2. 115/248 (46.4%) 3. 185/244 (75.8%) p<0.001 6-months: 1. 23.1%	27%/4 56%/2	D/C due to AE 1. 6% 2. 6% 3. 9% Bone density loss: 1. 1% 2. 2% 3. 7% Hot flush 1. 7% 2. 24%	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. IVR system; overall similar baseline characteristics and prognostic variables Performance Bias: Unclear. All subjects required to self-administer study drug twice a day; Elagolix identical in appearance to placebo; all patients took 2 doses per day of respective treatment; patients were blind to study drug allocation for the 6-month placebo-controlled portion of trial. High incidence of hot flush adverse effects in

	3. Elagolix 200 mg orally twice daily 6-month trial	-Premenopausal woman between 18 to 49 years of age -Diagnosis of endometriosis established by surgical documentation within prior 10 years -Moderate or severe pain for DYS and NMPP <u>Key Exclusion Criteria</u>: -Any clinically relevant gynecological surgical history -Any medical condition that makes the woman an unsuitable candidate per investigator discretion -Any chronic pain condition not caused by endometriosis -History of osteoporosis, bone fracture, or evidence of metabolic bone disease revealed by DXA scan Z-score < 1.5 for lumbar spine, femoral neck, or total hip at screening	3. 26%	2. 42.1% 3. 75.3% p <0.001 Proportion of women with a clinical response to non-menstrual pelvic pain as measured by the EDPID score at 3-months: 1. 136/373 (36.5%) 2. 125/248 (50.4%) 3. 133/244 (54.5%) p <0.001 6-months: 1. 34.9% 2. 45.7% 3. 62.1% p <0.001 <u>Key Secondary Endpoints</u>: Change from baseline on a 0- to 3-point dyspareunia pain scale: 1. -0.29 2. -0.39 (p=0.144; NS) 3. -0.49 (p<0.01) Dysmenorrhea EDPID score change at 6 months from baseline: 1. -0.44 2. -0.89 (p<0.001) 3. -1.75 (p<0.001) Non-menstrual Pelvic Pain EDPID score change at 6 months from baseline: 1. -0.31 2. -0.48 (p<0.001) 3. -0.72 (p<0.001) (All primary outcomes used 97.5% CI)	19%/6 52%/2 14%/8 18%/6 14%/8 18%/6 NA NA NA NA NA NA	3. 42% Headache 1. 10% 2. 15% 3. 17% Insomnia 1. 2% 2. 6% 3. 7% Night Sweats 1. 1% 2. 2% 3. 6% 95% CI and p-values NR for all outcomes		treatment groups versus placebo may have unblinded participants. <u>Detection Bias</u>: Low. All study site personnel and pathologists at central laboratories used for evaluation were blinded. <u>Attrition Bias</u>: Unclear. Overall 25%; modified intention-to-treat analysis performed with LOCF. 28% of subjects had protocol deviations which included entry, withdrawal, receipt of incorrect or wrong dose, and receipt of excluded concomitant treatments <u>Reporting Bias</u>: Unclear. Regression model used to determine responder status was not adequately described and/or reported; calculation of point threshold for definitions of DYS and NMPP responders not adequately described a priori; Imputation details for subjects in primary analysis not given; LOCF before 3-month assessment unknown effects on 6 month analysis; Sponsor designed the trial, analyzed the data, and wrote first draft of study manuscript. <u>Other Bias</u>: Numerous authors reports grant support and personal fees from multiple manufacturers including the sponsor during the conduct of the study and serve in leadership roles of relevant medical journals outside the submitted work. **Applicability**: <u>Patient</u>: Extensive exclusion criteria may limit generalizability due to lack of patients with depressive and/or psychiatric disorders; significant comorbidity exclusions left up to the discretion of the provider; women with history of osteoporosis or bone disorders excluded <u>Intervention</u>: Low-dose elagolix given once daily and high dose given twice daily; patients able to continue naproxen and/or select opioids (hydrocodone, codeine, tramadol +/- acetaminophen) concurrently throughout study <u>Comparator</u>: Placebo comparator <u>Outcomes</u>: Subjective pain diaries used to formulate response on modified unvalidated

								symptom assessment tool; MCID values not available for any pain instruments utilized in study; Setting: United States, Puerto Rico and Canada; Three quarters (74.8%) of the subjects were enrolled at study sites in the U.S. and Canada
Taylor, et al (Study M12-671; Elaris EM-2) Phase 3 RCT, DB, PC study of patients with endometriosis	1. Placebo 2. Elagolix 150 mg orally once daily 3. Elagolix 200 mg orally twice daily 6-month trial	Demographics: -Similar to EM-1 Key Inclusion Criteria: -Same as EM-1 study Key Exclusion Criteria: -Same as EM-1 study	ITT: 1. 360 2. 226 3. 229 PP: 1. 270 2. 178 3. 184 Attrition: 1. 25% 2. 21% 3. 20%	Primary Endpoints: Proportion of women with a clinical response to dysmenorrhea as measured by the EDPID score at 3-months: 1. 80/353 (22.7%) 2. 96/221 (43.4%) 3. 163/225 (72.4%) p <0.001 6 months: 1. 25.4% 2. 46.2% 3. 76.9% p<0.001 Proportion of women with a clinical response to non-menstrual pelvic pain as measured by the EDPID score at 3-months: 1. 129/353 (36.5%) 2. 110/221 (49.8%) 3. 130/225 (57.8%) p <0.001 6-months: 1. 40.6% 2. 51.6% 3. 62.2% Secondary Endpoints: Change from baseline on a 0- to 3-point dyspareunia pain scale: 1. -0.30 2. -0.39 (p=0.172; NS) 3. -0.60 (p<0.001)	 21%/5 50%/2 21%/5 52%/2 13%/8 21%/5 11%/10 22%/5 NA NA	D/C due to AE 1. 6% 2. 4% 3. 10% Bone density loss: 1. 1% 2. 2% 3. 7% Hot flush 1. 10% 2. 23% 3. 48% Headache 1. 14% 2. 19% 3. 23% Insomnia 1. 3% 2. 6% 3. 11% Total cholesterol % changes from baseline 1. -0.6 2. 4.6 3. 10.4	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. See EM-1 study Performance Bias: Unclear. See EM-1 study Detection Bias: Low. See EM-1 study Attrition Bias: Unclear. See EM-1 study; Overall 23%; 25% of subjects with protocol violations which included similar issues identified in EM-1 Reporting Bias: Unclear. See EM-1 study **Applicability**: Patient: See EM-1 study Intervention: See EM-1 study Comparator: See EM-1 study Outcomes: See EM-1 study; Setting: Argentina, Austria, Australia, Brazil, Czech Republic, Hungary, Italy, New Zealand, Poland, South Africa, Spain, the United States, and the United Kingdom; Three quarters (74.8%) of the subjects were enrolled at study sites in the U.S. and Canada

				Dysmenorrhea EDPID score change from baseline: 1. -0.52 2. -1.06 (p<0.001) 3. -1.65 (p<0.001) Non-menstrual Pelvic Pain EDPID score change from baseline: 1. -0.48 2. -0.63 (p<0.001) 3. -0.80 (p<0.001) (All primary outcomes used 97.5% CI)	 NA NA NA NA			
Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; DB = double-blinded; D/C = discontinuation; DXA = dual energy X-ray absorptiometry scan; DYS = dysmenorrhea; EDPID = Endometriosis Daily Pain Impact Diary; ITT = intention to treat; MCID = minimal clinically important difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NMPP = Non-menstrual pelvic pain; NR = not reported; NS = not significant; PC = placebo-controlled; PP = per protocol; RCT = randomized controlled trial.								

References:

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ORILISSA safely and effectively. See full prescribing information for ORILISSA.

ORILISSA™ (elagolix) tablets, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------
ORILISSA is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the management of moderate to severe pain associated with endometriosis. (1)

----------DOSAGE AND ADMINISTRATION----------
Normal liver function or mild hepatic impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months. (2.1)

Moderate hepatic impairment: 150 mg once daily for up to 6 months. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
Oral tablets: 150 mg and 200 mg (3)

----------CONTRAINDICATIONS----------
- Pregnancy (4)
- Known osteoporosis (4)
- Severe hepatic impairment (4)
- Strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (4)

----------WARNINGS AND PRECAUTIONS----------
- Bone Loss: Dose- and duration-dependent decreases in bone mineral density (BMD) that may not be completely reversible. Assess BMD in women with additional risk factors for bone loss (5.1)
- Reduced Ability to Recognize Pregnancy: ORILISSA may alter menstrual bleeding, which may reduce the ability to recognize pregnancy. Perform testing if pregnancy is suspected. Discontinue if pregnancy is confirmed (5.2)
- Suicidal Ideation and Mood Disorders: Advise patients to seek medical attention for suicidal ideation, suicidal behavior, new onset or worsening depression, anxiety, or other mood changes (5.3)
- Hepatic Transaminase Elevations: Dose-dependent elevations in serum alanine aminotransferase (ALT). Counsel patients on signs and symptoms of liver injury (5.4)
- Potential for Reduced Efficacy with Estrogen-Containing Contraceptives: Use non-hormonal contraception during treatment and for one week after discontinuing ORILISSA (5.5)

----------ADVERSE REACTIONS----------
Most common adverse reactions (>5%) in clinical trials included hot flushes and night sweats, headache, nausea, insomnia, amenorrhea, anxiety, arthralgia, depression-related adverse reactions and mood changes (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact AbbVie Inc. at 1-800-633-9110 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
See full prescribing information for a list of clinically important drug interactions (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 07/2018

Elagolix

Goal(s):

- Promote safe use of elagolix in women with endometriosis-associated pain.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:

- Initial: Up to 6 months
- Renewal: Up to 6 months for 150 mg daily dose with total cumulative treatment period not to exceed 24 months.

Requires PA:

- Elagolix

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy previously approved by the FFS program?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is this request for management of moderate to severe pain associated with endometriosis in a woman ≥18 years of age?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6

Approval Criteria		
6. Has the patient tried and failed an adequate trial of preferred first line therapy options including continuous administration of combined hormonal contraceptives or progestins alone +/- acetaminophen +/- non-steroidal anti-inflammatory drugs (NSAIDs) -or- Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity the first-line therapy options?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness • First-line therapy options such as hormonal contraceptives or progestins do not require PA
7. Does the patient have a diagnosis of osteoporosis or related bone-loss condition?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #8
8. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors? (e.g. cyclosporine, gemfibrozil, etc.)	**Yes:** Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have severe hepatic impairment as documented by Child-Pugh class C?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B?	**Yes:** Go to #11	**No:** Approve for 6 months
11. Is the dose for elagolix 150 mg once daily?	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been receiving therapy with elagolix 150 mg once daily?	**Yes:** Go to #2	**No:** Pass to RPh; Deny; medical appropriateness. (Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling)
2. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B?	**Yes:** Pass to RPh; Deny; medical appropriateness. (Elagolix 150 mg once daily is limited to 6-month maximum treatment duration in patients with moderate hepatic impairment per FDA labeling)	**No:** Go to #3
3. Has the patient's condition improved as assessed and documented by the prescriber?	**Yes:** Approve for up to 6 months. Total cumulative treatment period not to exceed 24 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.