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# Prior Authorization Criteria Update: Myfembree (Relugolix, Estradiol, and Norethindrone) (Gonadotropin-Releasing Hormone Antagonists)

**Plain Language Summary:**

- Does the new indication for relugolix, estradiol, and norethindrone combination therapy impact current Medicaid policies for medicines used to treat pain associated with endometriosis?
- Endometriosis is a chronic and painful disease that occurs when endometrium (tissue the originates from the lining of the uterus) starts growing outside of the uterus where it does not belong. Estrogen, a female sex hormone, causes this tissue to grow. Later in the menstrual cycle, these patches of endometrial tissue (or lesions) may break down and shed the in the body. This can cause pain throughout the entire month. The most common symptoms of endometriosis include painful periods, pelvic pain between periods, and pain with sexual intercourse. Endometriosis can also cause infertility, or difficulty getting pregnant.
- The most common treatments to relieve pain associated with endometriosis are hormone therapies. Hormone therapies are medicines that decrease the amount of estrogen in the body. Less estrogen will slow the growth of endometrial tissue and stop more lesions from forming outside the uterus. Certain kinds of birth control pills (such as estradiol combined with norethindrone), and medicines called gonadotropin-releasing hormone blockers, stop the production of hormones that tell the ovaries to make estrogen, which decreases the amount of endometrial tissue that grows every month. Many people have lighter and shorter menstrual flows (periods) when they take birth control pills. The gonadotropin-releasing hormone blockers may create an artificial menopause, and monthly periods are prevented.
- Relugolix, estradiol, and norethindrone is a combination gonadotropin-releasing hormone blocker and birth control pill. The side effects of relugolix include symptoms of menopause such as hot flashes, vaginal dryness, and bone loss. Adding the birth control pill may decrease some of these side effects. The risk of bone loss when taking relugolix is very high, which prevents people from taking this medicine longer than 24 months.
- Two 3-month studies showed relugolix combined with estradiol and norethindrone relieved menstrual pain and pelvic pain between periods better than people that did not take any medicine.
- Providers must explain to the Oregon Health Authority (OHA) why a patient needs relugolix, estradiol, norethindrone combination therapy before Medicaid will pay for it. This process is called prior authorization.
- Fee-for-service (FFS) Medicaid pays for birth control pills when prescribed for adolescents and adults and does not require prior authorization.
- The OHA recommends changing the PA policy to include pain associated with endometriosis as a reason to prescribe relugolix, estradiol and norethindrone combination therapy.

**Purpose of Update:**

- Review evidence for the expanded Food and Drug Administration (FDA)-approved indication for relugolix, estradiol, and norethindrone combination therapy (MYFEMBREE) to manage moderate to severe pain associated with endometriosis.

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**Recommendation:**

- Revise prior authorization (PA) criteria for relugolix, estradiol, and norethindrone combination therapy to include management of moderate to severe pain associated with endometriosis in premenopausal women (**Appendix 1**).

**Background:**

The gonadotropin-releasing hormone antagonists (GnRH) were last reviewed by the Pharmacy and Therapeutics (P & T) committee in December 2021. At that time, a class update was presented which reviewed comparative evidence for safety and efficacy of oral contraceptives, progestins, GnRH agonists, danazol, and GnRH antagonists for management of moderate to severe pain due to endometriosis. In addition, evidence supporting FDA approval for relugolix, estradiol, and norethindrone combination therapy for management of heavy menstrual bleeding associated with uterine fibroids in premenopausal populations was evaluated. The P & T Committee approved recommendations to maintain relugolix combination therapy as non-preferred on the preferred drug list (PDL) and implement new prior authorization (PA) criteria for GnRH modifiers to evaluate GnRH antagonists, including relugolix, estradiol, and norethindrone combination therapy, separately from GnRH agonists (e.g., leuprolide).

The goal of endometriosis management is to prevent disease progression and improve patient's quality of life.[1] Although 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.[1] Medical therapy for endometriosis is based on the observation that ectopic tissue is hormonally responsive.[2] Drugs that suppress ovulation have been found to be beneficial in managing the pain associated with endometriosis. Danazol, an anabolic steroid which inhibits gonadotropin secretion, was the first FDA-approved agent for endometriosis, but its usefulness has been undermined by a significant adverse effect profile.[3] Current first-line therapies to manage pain associated with endometriosis are continuous combined oral contraceptives (COCs) or progestin.[4] Oral contraceptives have been shown to suppress gonadotropin secretion and estrogen biosynthesis.[3,5] Most of the data supporting the use of COCs in managing endometriosis pain is observational.[4]

Second-line therapeutic options for pain associated with endometriosis are GnRH agonists administered with hormone therapy or in combination with a levonorgestrel-releasing intrauterine device (LNG-IUD).[4] Gonadotropin-releasing hormones (i.e. goserelin, leuprolide, and nafarelin) initially stimulate the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), resulting in a temporary increase of ovarian steroidogenesis.[2] However, continuous administration of GnRH agonists in women results in suppression of gonadotropin secretion and decreased steroidogenesis of estrogen.[3,5] Goserelin, leuprolide, and nafarelin are FDA-approved for six months of continuous use for treatment of pelvic pain caused by endometriosis.[3] The six-month treatment limitation is due to concern about the significant bone loss that occurs with GnRH agonist therapy. Add-back therapy or the simultaneous use of estrogen and progestin, progestin alone, or progestin plus a bisphosphonate may alleviate some of the GnRH agonist side effects including bone loss.[4] The FDA recommends the use of add-back therapy (estrogen, progestin, bisphosphonates) when a GnRH agonist is used for greater than 6 months.[4]

Elagolix and relugolix are GnRH receptor antagonists. Both drugs competitively bind to pituitary GnRH receptors, blocking binding of endogenous GnRH with reversible, dose-dependent suppression of LH and FSH, and ovarian estradiol and progesterone production.[6,7] The oral GnRH antagonist, elagolix, reduces moderate-to-severe endometriosis-associated pain and is FDA-approved as a once-daily low dose or a twice-daily high dose.[6] However, hypoestrogenic-induced declines in bone mineral density mean that elagolix treatment is a maximum duration of 24 months for a low dose (6 months in patients with moderate hepatic impairment) and 6 months for a high-dose regimen.[6] Relugolix combination therapy (40 mg relugolix, 1 mg estradiol, and 0.5 mg norethindrone) was developed as a once-daily treatment for uterine fibroids, and recently received FDA-approval for management of pain associated with endometriosis.[7] Use of relugolix

combination therapy should be limited to 24 months due to the risk of continued bone loss that may not be reversible.[7] **Table 1** outlines the pharmacotherapies approved by the FDA for management of moderate to severe pain associated with endometriosis.

**Table 1. FDA-Approved Medications for Management of Pain Associated with Endometriosis**[8]

| Drug Name (Brand Name) | Formulation | FDA-Approved Endometriosis Dose and Frequency | Safety Precautions (Boxed Warning in Bold) |
|---|---|---|---|
| ***Anabolic Steroid*** | | | |
| Danazol (DANOCRINE) | Oral Capsule: 50 mg, 100 mg, 200 mg | Initial, mild disease: 200 to 400 mg PO given in 2 divided doses; adjust depending on clinical response<br><br>Moderate to severe disease: 800 mg PO in 2 divided doses; titrate downward depending on clinical response<br><br>Duration: 3-6 months, may be extended to 9 months if necessary | **-Thrombotic events including strokes**<br>**-Peliosis hepatis and benign hepatic adenoma**<br>**-Intracranial hypertension**<br>**-Use in pregnancy is contraindicate**d<br>-Lipoprotein changes<br>-Androgen effects |
| ***Gonadotropin Releasing Hormone Agonists*** | | | |
| Goserelin acetate (ZOLADEX) | Subcutaneous Implant: 3.6 mg | 1.6 mg SC every 28 days<br><br>Duration: 6 months maximum | -Hyperglycemia<br>-Loss of BMD<br>-Hypoestrogenism<br>-Serum lipid changes<br>-Use in pregnancy is contraindicated |
| Leuprolide acetate (LUPRON-DEPOT) | Intramuscular depot Injection:<br>1-month: 3.75 mg<br>3-month: 11.25 mg | 3.75 mg IM monthly for 6 months<br>OR<br>11.25 mg IM every 3 months for 1 or 2 doses<br><br>Duration: 6 months maximum | -Loss of BMD<br>--Use in pregnancy is contraindicated |
| Nafarelin acetate (SYNAREL) | Nasal Spray: 200 mcg/actuation | 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 starting between days 2 and 4 of the menstrual cycle (maximum daily dose = 800 mcg)<br><br>Duration: 6 months | -Loss of BMD<br>-Worsening depression<br>-Hypoestrogenism<br>-Serum lipid changes<br>-Use in pregnancy is contraindicated |
| ***Progestins*** | | | |
| Medroxyprogesterone acetate (DEPO-SUBQ PROVERA) | Subcutaneous Depot Injection: 104 | 104 mg SC every 12 to 14 weeks<br><br>**Duration: Do not use for longer than 2 years (boxed warning)** | **-Loss of BMD**<br>-Ocular disorders (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine)<br>-Ectopic pregnancy<br>-Menstrual bleeding irregularities<br>-Use in pregnancy is contraindicated |

| | | | |
|---|---|---|---|
| Norethindrone Acetate (AYGESTIN) | Oral Tablet: 5mg | 5 mg PO once daily for 2 weeks; increase dose by 2.5 mg per day every 2 weeks until 15 mg once daily is achieved<br><br>Duration: 6 to 9 months or until breakthrough bleeding demands temporary termination | -Ocular disorders (sudden loss of vision, or sudden onset of proptosis, diplopia, or migraine)<br><br>-Worsening depression<br>-Increased risk for thrombosis<br>-Bleeding irregularities<br>-Ectopic pregnancy<br>-Adverse effects on lipid metabolism<br>-Use in pregnancy is contraindicated |
| ***Gonadotropin-Releasing Hormone Antagonists*** | | | |
| Elagolix (ORILISSA) | Oral Tablet: 150 mg, 200 mg | Initial: 150 mg PO once daily<br>OR<br>Concomitant dyspareunia: 200 mg PO twice daily<br><br>Moderate hepatic impairment: 150 mg once daily<br><br>Duration of therapy: 24 months (150 mg, normal/mild hepatic impairment); 6 months (200 mg, normal/mild hepatic impairment OR 150 mg, moderate hepatic impairment) | -Decreased BMD<br>-Suicidal ideation<br>-Hepatic transaminase elevations<br>-Use in pregnancy is contraindicated |
| Relugolix, estradiol, and norethindrone (MYFEMBREE) | Oral Tablet: relugolix 40 mg, estradiol 1 mg, & norethindrone 0.5 mg | 1 fixed-dose combination tablet PO once daily<br><br>Duration of therapy: 24 months | -**Thromboembolic disorders and vascular events**<br>-Decreased BMD<br>-Breast cancer or other hormone-sensitive malignancies<br>-Suicidal ideation and mood disorders<br>-Hepatic impairment or transaminase elevations<br>-Gallbladder disease or history of cholestatic jaundice<br>-Hypertension<br>-Menstrual bleeding irregularities<br>-Use in pregnancy is contraindicated |
| Abbreviations: BMD = bone mineral density; FDA = Food and Drug Administration; IM = intramuscular; mcg = microgram; mg = milligram; PO = oral; SC = subcutaneous | | | |

There are several non-specific assessment scales that have been used to measure patient response to endometriosis medical treatment intervention. For pain assessment, an 11-point numeric rating scale (NRS) which ranges from a score of 0 (no pain symptoms) to 10 (worst pain imaginable) has been used.[9] 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.[9] Pain and/or symptom scales that have been developed specifically for endometriosis often have substantial limitations, inconsistencies, or lack validation.[10]

The FDA approval for the use of relugolix in management of moderate to severe pain associated with endometriosis was based on two 24-week, phase 3, placebo-controlled, double-blind, randomized controlled trials (RCTs), SPIRIT 1 and 2.[11] The 2 RCTs were conducted in 219 research centers in Africa, Australia, Europe, North America, and South America.[11] Four centers were located in the United States, and 5 centers were based on Poland; all the other countries included only 1 study location.[11] Pre-menopausal women aged 18 to 50 years with moderate to severe pain associated with surgically or directly visualized endometriosis with or without histological confirmation, or histological diagnosis alone within the past 10 years, were eligible for study enrollment.[11] Inclusion criteria included a dysmenorrhea NRS score of 4.0 or higher on 2 or more days and a mean non-menstrual pelvic pain NRS score of 2.5 or higher, or a mean score of 1.25 or higher that included a score of 5.0 or greater on 4 or more days.[11] Patients were excluded from the study if they had a bone mineral density Z-score of less than -2.0 at the lumbar spine, total hip or femoral neck; a history of chronic pelvic pain not caused by endometriosis; or a contradiction to the use of combined hormonal therapy.[11]

Patients were randomized 1:1:1 to receive the relugolix combination product for 24 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for 12 weeks followed by relugolix combination therapy for 12 weeks (delayed relugolix combination therapy).[11] The delayed relugolix combination therapy group was included to compare bone mineral density and vasomotor symptoms for relugolix monotherapy with relugolix combination therapy at week 12.[11] SPIRIT 1 enrolled 638 patients to receive relugolix combination therapy (n=212), placebo (n=213), or relugolix delayed combination therapy (n=213).[11] SPIRIT 2 enrolled 623 patients were enrolled to receive relugolix combination therapy (n=208), placebo (n=208), or relugolix delayed combination therapy (n=207).[11] The co-primary endpoints were responder rates at week 24 for dysmenorrhea and non-menstrual pelvic pain, both based on NRS scores and analgesic use.[11] Eligible patients who completed the SPIRIT studies could enroll in a currently ongoing 80-week open-label extension study (SPIRIT EXTENSION) for post-treatment follow-up for safety, specifically for bone mineral density and menses recovery.[11] Twenty-nine percent (n=185) of patients in SPIRIT 1 and 47% (n=288) in SPIRIT 2 were taking opioids (i.e., tramadol 50 mg, codeine 30 mg, or hydrocodone 5 mg; prescribed according respective country's approved product labeling) for pain relief at baseline.[11] Most of the women enrolled in the studies were White (90%), with a mean age of 34 years.[11] Fifteen percent (n=98) of patients terminated study participation early in SPIRIT 1 and 18% (n=118) in SPIRIT 2.[11] Reasons for early termination included adverse events, protocol deviations, loss to follow-up, withdrawal of consent, lack of efficacy, or pregnancy.[11] Withdrawal of consent was the most common reason for study withdrawal.

Responder criteria was defined as achieving a mean reduction in dysmenorrhea NRS score of at least 2.8 points and a mean reduction in nonmenstrual pelvic pain NRS score of at least 2.1 points at week 24 and no increase in use of analgesic medication as recorded in a daily electronic diary.[11] In SPIRIT 1, 74.5% of patients in the relugolix combination therapy group met the dysmenorrhea responder criteria compared with 26.9% patients in the placebo group (treatment difference 47.6%; 95% confidence interval [CI] 39.3 to 56.0; p<0.0001).[11] In SPIRIT 2, 75.1% of patients in the relugolix combination therapy group were dysmenorrhea responders compared with 30.5% of patients in the placebo group (treatment difference 44.6%; 95% CI 35.9 to 53.3; p<0.0001).[11] In SPIRIT 1, 58.5% of patients in the relugolix combination therapy group met the non-menstrual pelvic pain responder criteria versus 39.6% of patients in the placebo group (treatment difference 18.9%; 95% CI 9.5 to 28.2; p<0.0001).[11] In SPIRIT 2, 65.9% of patients were non-menstrual pelvic pain responders in the relugolix combination therapy group compared with 42.5% of patients in the placebo group (treatment difference 23.4%; 95% CI 13.9 to 32.8; p<0.0001).[11] Proportions of responders treated with relugolix combination therapy over 24 weeks compared with placebo-treated responders are summarized in **Table 2**.

**Table 2. Proportions of Dysmenorrhea and Non-Menstrual Pelvic Pain Responders at Week 24**[7]

| | **Spirit 1** | | **Spirit 2** | |
|---|---|---|---|---|
| | Relugolix 40 mg, estradiol 1 mg, & norethindrone 0. 5mg (n=212) | Placebo (n=212) | Relugolix 40 mg, estradiol 1 mg, & norethindrone 0.5 mg (n=205) | Placebo (n=200) |

| | | | | |
|---|---|---|---|---|
| Dysmenorrhea | 74.5% (n=158) | 26.9% (n=57) | 75.1% (n=154) | 30.5% (n=61) |
| Difference from Placebo<br>95% Confidence Interval<br>p-value | 47.6%<br>39.3% to 56.0%<br>p<0.0001 | | 44.6%<br>35.9% to 53.3%<br>p<0.0001 | |
| | | | | |
| Non-menstrual pelvic pain | 58.5% (n=124) | 39.6% (n=84) | 65.9% (n=136) | 42.5% (n=87) |
| Difference from placebo<br>95% Confidence Interval<br>p-value | 18.9%<br>9.5% to 28.2%<br>p<0.0001 | | 23.4%<br>13.9% to 32.8%<br>p<0.0001 | |

The most common adverse events reported in the 2 trials were headache, nasopharyngitis, and hot flushes.[11] There were 9 reports of suicidal ideation across both studies (two in the placebo run-in, two in the placebo group, two in the relugolix combination therapy group, and three in the delayed relugolix combination therapy group).[11] No deaths were reported.[11] Least squares mean percentage change in lumbar spine bone mineral density in the relugolix combination therapy versus placebo groups was –0.70% versus 0.21% in SPIRIT 1 and –0.78% versus 0.02% in SPIRIT 2, and in the delayed relugolix combination group was –2.0% in SPIRIT 1 and –1.9% in SPIRIT 2.[11] Decreases in opioid use were seen in cotreated patients compared with placebo.[11]

The SPIRIT studies had limitations. Although the trial population included people with moderate-to-severe endometriosis-associated pain, many screened individuals did not meet the minimum pelvic pain threshold to participate.[11] Most patients enrolled were White, potentially reflecting under-recognition or under-diagnosis of endometriosis, or suboptimal clinical trial engagement among other races and ethnicities.[11] Treatment duration was 6 months, and these studies cannot address efficacy and safety beyond this period.[11] Use of a placebo-controlled study design did not allow for comparison with mainstays of treatment, including hormonal therapies or surgery. However, because the studies were multinational, an active comparator would have to be an approved endometriosis treatment for all countries participating in the study.[11]

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**Appendix 1.** Proposed PA Revisions

# Gonadotropin-Releasing Hormone Antagonists

## Goal(s):

- Promote safe use of elagolix and relugolix/estradiol/norethindrone in people with endometriosis-associated pain
- Promote safe use of elagolix/estradiol/norethindrone and relugolix/estradiol/norethindrone for heavy menstrual bleeding associated with uterine fibroids (leiomyoma).
- Promote use that is consistent with medical evidence and product labeling.

## Length of Authorization:

- Initial: Up to 6 months
- Elagolix renewal: Up to 6 months for 150 mg daily dose with total cumulative lifetime treatment period not to exceed 24 months in patients with normal hepatic function. For patients with moderate hepatic impairment receiving 150 mg once daily, duration of

therapy should not exceed 6 months. In patients receiving high dose elagolix therapy (200 mg twice daily), maximum treatment duration is 6 months.

- Elagolix/estradiol/norethindrone renewal: Up to 6 months for elagolix 300 mg dosed twice daily with a total cumulative treatment period not to exceed 24 months
- Relugolix/estradiol/norethindrone renewal: Up to 6 months for relugolix component 40 mg dosed once daily with a total cumulative treatment period not to exceed 24 months

**Requires PA:**

- Elagolix (ORLISSA)
- Elagolix/estradiol/norethindrone (ORIAHNN)
- Relugolix/estradiol/norethindrone (MYFEMBREE)

**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 the patient pregnant or actively trying to conceive? | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #5 |

| Approval Criteria | | |
|---|---|---|
| 5. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant? | **Yes:** Go to #6 | **No:** Pass to RPh. Deny; medical appropriateness |
| 6. Is this request for management of moderate to severe pain associated with endometriosis in a premenopausal patient? | **Yes**: Go to #7 | **No:** Go to #13 |
| 7. Has the patient tried and failed an adequate trial of preferred first line endometriosis therapy options including administration of combined hormonal contraceptives or progestins (oral, depot injection, or intrauterine) alone?<br>-or-<br>Does the patient have a documented intolerance, FDA- labeled contraindication, or hypersensitivity the first-line therapy options? | **Yes:** Go to #8 | **No:** Pass to RPh. Deny; medical appropriateness<br>• First-line therapy options such as combined hormonal contraceptives or progestins do not require PA |

| Approval Criteria | | |
|---|---|---|
| 8. Is the patient taking any concomitant medications that are strong organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine, gemfibrozil, etc.), combined P-glycoprotein inhibitor and moderate CYP3A inhibitor (e.g., erythromycin), combined P-glycoprotein inducer and strong CYP3A inducer (e.g., rifampin)?<br><br>Note: Elagolix levels are increased when co-administered with OATP1B1 inhibitors. Relugolix levels are increased when co-administered with inhibitors such as erythromycin and decreased when co-administered with inducers such as rifampin. Avoid combinations of these therapies due to drug interactions that can increase the risk of adverse reactions or decrease the efficacy of GnRH antagonists. | **Yes:** Deny; medical appropriateness | **No:** Go to #9 |
| 9. Does the patient have a diagnosis of osteoporosis or related bone-loss condition?<br><br>Note: In patients with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH antagonists may pose an additional risk, and the risks and benefits should be weighed carefully. | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #10 |
| 10. Does the patient have severe hepatic impairment as documented by Child-Pugh class C? | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Go to #11 |

| Approval Criteria | | |
|---|---|---|
| 11. Does the patient have moderate hepatic impairment as documented by Child-Pugh class B? | **Yes:** Go to #12 | **No:** Approve for 6 months<br><br>***** FDA approved elagolix dosing for patients with normal liver function or mild liver impairment: 150 mg once daily for up to 24 months or 200 mg twice daily for up to 6 months |
| 12. Is the dose for elagolix 150 mg once daily or relugolix 40 mg /estradiol 1 mg/norethindrone 0.5 mg? | **Yes:** Approve for 6 months (cumulative lifetime treatment)<br><br>***** FDA approved elagolix dosing for moderate hepatic impairment: 150 mg once daily for up to 6 months. | **No:** Pass to RPh. Deny; medical appropriateness |
| 13. Is the request for elagolix/estradiol/norethindrone or relugolix/estradiol/norethindrone for management of heavy menstrual bleeding associated with uterine fibroids (leiomyomas)? | **Yes:** Go to #14 | **No:** Pass to RPh. Deny; medical appropriateness |

| Approval Criteria | | |
|---|---|---|
| 14. Has the patient tried and failed a trial of first line therapy options including at least 1 of the following for at least 3 months:<br>a) hormone-releasing IUD OR<br>b) continuous administration of combined hormonal contraceptives OR<br>c) cyclic progestins OR<br>d) tranexamic acid?<br>OR<br>Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the first-line therapy options? | **Yes**: Go to #15 | **No:** Pass to RPh. Deny; medical appropriateness<br><br>First-line therapy options such as hormonal contraceptives, progestins, or tranexamic acid do not require PA |
| 15. Does the patient have a diagnosis of osteoporosis or related bone-loss condition?<br><br>Note: In patients with major risk factors for decreased bone mineral density (BMD) such as chronic alcohol (> 3 units per day) or tobacco use, strong family history of osteoporosis, or chronic use of drugs that can decrease BMD, such as anticonvulsants or corticosteroids, use of GnRH antagonists may pose an additional risk, and the risks and benefits should be weighed carefully. | **Yes:** Pass to RPh. Deny; medical appropriateness | **No:** Approve for 6 months (cumulative, lifetime treatment) |

| Renewal Criteria | | |
|---|---|---|
| 1. Has the patient been receiving elagolix/estradiol/norethindrone for management of uterine fibroids or relugolix/estradiol/norethindrone for management of uterine fibroids or pain associated with endometriosis? | **Yes:** Go to #4 | **No:** Go to #2 |

| Renewal Criteria | | |
|---|---|---|
| 2. Has the patient been receiving therapy with elagolix 150 mg once daily for management of endometriosis? | **Yes:** Go to #3 | **No:** Pass to RPh; Deny; medical appropriateness.<br><br>(Elagolix 200 mg twice daily is limited to 6-month maximum treatment duration per FDA labeling) |
| 3. Does the patient have moderate hepatic impairment as documented by Child-Pugh Class B? | **Yes:** Pass to RPh; Deny; medical appropriateness.<br><br>(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 #4 |
| 4. Has the patient's condition* improved as assessed and documented by the prescriber?<br><br>*For endometriosis: has pain associated with endometriosis improved?<br>For uterine fibroids: has patient experienced at least a 50% reduction in menstrual blood loss from baseline? | **Yes:** Approve for up to 18 months<br><br>Document physician attestation received.<br><br>Total cumulative treatment period not to exceed 24 months. | **No:** Pass to RPh; Deny; medical appropriateness. |

*P&T/DUR Review: 2/23; 12/21 (DM), 3/19 (DM),11/18 (DE)*
*Implementation: 4/1/23; 1/1/22; 5/1/19*