GnRH Antagonists for Gynecologic Conditions
EOCCO POLICY

Policy Type: PA Pharmacy Coverage Policy: EOCCO021

Description
Elagolix and relugolix are oral gonadotropin-releasing hormone (GnRH) antagonists.

Length of Authorization
- Initial: Three months
- Renewal:
  i. Elagolix (Orilissa) 150 mg: Up to 12 months; maximum total (lifetime) fills should not exceed #24 30-day fills
  ii. Elagolix (Orilissa) 200 mg: Up to three months; maximum total (lifetime) fills should not exceed #6 30-day fills
  iii. Elagolix/estradiol/norethindrone acetate (Oriahnn) and relugolix/estradiol/norethindrone (Myfembree): Up to 12 months; maximum total (lifetime) fills should not exceed #24 28-day fills

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
elagolix (Orilissa)	Moderate to severe pain associated with endometriosis	150mg tablets	30 tablets/30 days
		200mg tablets	60 tablets/30 days
elagolix/estradiol/ norethindrone acetate (Oriahnn)	Treatment of heavy menstrual bleeding associated with uterine fibroids	300 mg/1 mg/0.5 mg tablets	56 tablets/28 days
relugolix/estradiol/ norethindrone (Myfembree)	Heavy menstrual bleeding associated with uterine fibroids (leiomyoma) Moderate to severe pain associated with endometriosis	40 mg/1 mg/0.5 mg tablets	28 tablets/28 days

Initial Evaluation

I. **Elagolix (Orilissa), elagolix/estradiol/norethindrone acetate (Oriahnn) and relugolix/estradiol/norethindrone (Myfembree)** may be considered medically necessary when the following criteria below are met:

A. Member is 18 years of age or older; **AND**
B. Medication is prescribed by, or in consultation with, an obstetrician/gynecologist; **AND**
C. Member does **not** have history of osteoporosis (defined as a T-score less than or equal to -2.5 or Z-score less than -1.5 at the lumbar spine, femoral neck or total hip); **AND**
D. Provider attestation that the member has not previously been treated with a full course of a GnRH antagonist (i.e., Orilissa, Oriahnn, Myfembree); **AND**
E. A diagnosis of one of the following:
    1. **Moderate-to-severe pain associated with endometriosis; AND**
        i. Request is for elagolix (Orilissa) or relugolix/estradiol/norethindrone (Myfembree); **AND**
        ii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
            a. Nonsteroidal anti-inflammatory drugs (NSAIDs); **OR**
            b. Hormonal contraceptives (oral, IUD, implant, etc.); **AND**
        iii. If the request is for elagolix (Orilissa) and continued use of estrogen containing contraceptives is planned in combination, the provider acknowledges that the efficacy of both the contraceptive and elagolix (Orilissa) may be decreased (use of non-hormonal contraceptives is recommended); **OR**
    2. **Heavy menstrual bleeding associated with uterine fibroids; AND**
        i. Request is for elagolix/estradiol/norethindrone acetate (Oriahnn) or relugolix/estradiol/norethindrone (Myfembree); **AND**
        ii. At least one hormonal contraceptive (oral, IUD, implant, etc.) has been ineffective, not tolerated, or ALL are contraindicated; **AND**
        iii. Treatment with tranexamic acid has been ineffective, not tolerated, or is contraindicated

II. Elagolix and/or relugolix is considered investigational when used for all other conditions, including but not limited to:
    A. Polycystic ovary syndrome
    B. Fertility treatment

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If so, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

III. Provider attestation that the member has not previously received treatment with a full course of a GnRH antagonist (i.e., Orilissa, Oriahnn, Myfembree); **AND**

IV. **Elagolix (Orilissa)**:
   A. Member has experienced a clinical improvement in pain symptoms relating to endometriosis; **AND**
      1. If the request is for elagolix (Orilissa) 150 mg; the member has not received treatment with elagolix (Orilissa) 150 mg for more than 24 months; **OR**
      2. If the request is for elagolix (Orilissa) 200 mg**;** the member has not received treatment with elagolix (Orilissa) 200 mg for more than 6 months; **OR**

V. **Elagolix/estradiol/norethindrone acetate (Oriahnn)**:
   B. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improved quality of life, etc.); **AND**
      1. The member has not received treatment for more than 24 months

VI. **Relugolix/estradiol/norethindrone (Myfembree):**
   C. Member has exhibited improvement in symptoms (reduction in menstrual blood loss, pain reduction, improved quality of life, etc.); **AND**
      1. The member has not received treatment for more than 24 months

Supporting Evidence

I. Elagolix and Relugolix combination oral gonadotropin-releasing hormone (GnRH) antagonists have been evaluated in several clinical trials in adults. The safety and efficacy in pediatric patients have not been established and FDA approvals for these agents are limited to adult members.

II. Endometriosis and uterine fibroids are complex diseases and given the potential for long term side effects of GnRH antagonists, supervision of treatment/consultation by a gynecologist or obstetrician is required.

III. Clinical trials evaluating elagolix with or without estradiol/norethindrone excluded patients with a Z-score less than -1.5 at the lumbar spine, femoral neck, or total hip. Bone loss of more than 5% was seen in lumbar spine, total hip, and femoral neck within six months of treatment. Clinical trials evaluating relugolix/estardiol/norethindrone (Myfembree) excluded patients with Z-score less than -2.0 at the lumbar spine, femoral neck, or total hip. Bone loss of approximately 1% was seen in the lumbar spine within 6 months and consistent through 2 years of treatment. Bone loss studies have not yet been completed to evaluate elagolix (Orilissa) and elagolix/estradiol/norethindrone acetate (Oriahnn) in combination with bone loss prevention treatments.

IV. **Elagolix (Orilissa)** is an oral GnRH antagonist for the management of moderate to severe pain associated with endometriosis. The drug was studied in two randomized, double-blind, placebo-controlled, Phase 3, trials (Study EM-1 and Study EM-2; Elaris Endometriosis I and II).
- At three months, both elagolix (Orilissa) 150 mg and 200 mg regimens showed a higher proportion of responders compared to placebo. Both treatment arms showed statistically significant differences in greater mean decreases in non-menstrual pelvic pain scores from baseline at six months.
- The FDA-approved maximum duration of use for 150 mg tablets is 24 months, though clinical trials only studied up to 12 months. The FDA-approved maximum duration of use for 200 mg tablets is six months. These FDA maximum durations of treatment are recommended due to loss of bone marrow density as seen in clinical trials. Bone loss of more than 5% was seen in lumbar spine, total hip, and femoral neck within six months of treatment. Studies have not yet been completed to evaluate in combination with bone loss prevention treatments.
- Due to the mechanism of action, use of estrogen containing contraceptives are expected to reduce the efficacy of elagolix (Orilissa); likewise, use of elagolix (Orilissa) will reduce efficacy of estrogen containing oral contraceptives. To avoid drug interactions, use of non-hormonal contraceptives during treatment with elagolix (Orilissa) is recommended.

V. For the treatment of heavy menstrual bleeding associated with uterine fibroids there is a lack of randomized trial data demonstrating the effectiveness of medical therapies. Treatment options include hormonal contraceptives (oral, IUD, implant, etc.), ulipristal acetate (Ella), mifepristone (Korlym, Mifeprex), GnRH agonists (leuprolide depot (Lupron), nafarelin acetate (Synarel), goserelin acetate (Zoladex), etc.), raloxifene (Evista), and danazol. GnRH agonists are an effective medical therapy but due to side effects are primarily used as preoperative therapy. Surgical treatment options are available, but often patients become incapable of reproduction.

VI. Uterine fibroids are commonly experienced by women that are premenopausal, and are associated with heavy menstrual bleeding, pain, and anemia. Management strategies for uterine fibroids include hysteroscopic fibroid resection, estrogen-progestin contraceptives, progestin-releasing intrauterine devices, progestin-only contraceptives, tranexamic acid, GnRH agonists (e.g., Lupron), GnRH antagonists (e.g., Oriahnn, Myfembree), uterine artery embolization, hysterectomy, and endometrial ablation.

VII. Treatment choice is dependent on fibroid size, patient age, fertility preference, symptoms, and other patient related factors. Hysterectomy is the only definitive cure, but myomectomy may be preferred for women with submucosal fibroids wishing to preserve the uterus. Medication therapy may be preferred for management to either prolong time to surgery or as preoperative treatment in preparation for surgery. Given the complex treatment choices and risks associated with each, therapy should be directed by or in consultation with a specialist.

VIII. The most common medication therapy utilized for the management of uterine fibroids includes estrogen-progestin contraceptives (e.g., pills, rings, patches) and progestin IUDs. These

interventions do not change affect the pathology of the fibroids, but they are accepted as a standard management strategy to reduce the heavy menstrual bleeding. Tranexamic acid is a nonhormonal treatment that may be used during menstruation to reduce heavy bleeding.

IX. As the safety profiles often limit their use, GnRH agonists and antagonists are second-line medications. GnRH agonists (e.g., Lupron) are often used for a few months preoperatively to reduce fibroid size, or to bridge a patient into menopause. For GnRH antagonists, there are two products available: relugolix/estradiol/norethindrone (Myfembree), and elagolix/estradiol/norethindrone (Oriahnn). Acute tolerability is generally more favorable, but long-term safety and efficacy data are limited. Additionally, there is a known decrease in bone mineral density (BMD) which limits treatment duration. Furthermore, the safety of utilizing GnRH antagonists subsequently at their full FDA-approved duration is unknown, and would be expected to exacerbate the decrease in BMD.

X. For the treatment of pain associated with endometriosis there are no studies supporting one treatment, or treatment combination, over another. Treatment choice is based upon symptom severity, patient preferences, medication side effects, treatment efficacy, contraceptive needs, costs, and availability. Treatments commonly used first-line are NSAIDs and continuous hormonal contraceptives because these therapies are low-risk, have few side effects, and provide relief of symptoms for many women. Second-line treatments include GnRH agonists (leuprolide depot (Lupron), nafarelin acetate (Synarel), goserelin acetate (Zoladex), etc.), progestins, and danazol.

XI. **Elagolix/estradiol/norethindrone acetate (Oriahnn)** was evaluated in two six-month, randomized, double-blind, placebo-controlled, Phase 3 trials (Elaris UF-1 and Elaris UF-2) and one six-month, extension trial (Elaris UF-EXTEND). The primary efficacy outcome was the percentage of women who had menstrual blood loss (MBL) volume <80 mL during the final month and ≥ 50% reduction in MBL volume from baseline to the final month.

- In Elaris UF-1, the primary outcome was 68.5%, 84.1%, and 8.7% ($p<0.001$) for elagolix/estradiol/norethindrone acetate (Oriahnn) plus hormonal therapy, elagolix alone, and placebo, respectively. In Elaris UF-2, the primary outcome was 76.5%, 76.9%, 10.5% ($p<0.001$) for elagolix/estradiol/norethindrone acetate (Oriahnn), elagolix alone, and placebo, respectively. In Elaris UF-EXTEND, the primary outcome was 87.9% for elagolix/estradiol/norethindrone acetate (Oriahnn). The hormonal therapy that was used in combination with elagolix was estradiol/norethindrone (Activella, Amabelz, Combipatch, Lopreeza, Mimvey Lo, and Mimvey).
- The most common adverse events noted for elagolix/estradiol/norethindrone acetate (Oriahnn) were hot flashes, night sweats, nausea, and headache; however, elagolix/estradiol/norethindrone acetate (Oriahnn) had lower rates of hot flashes and night sweats compared to elagolix (Orilissa). Elagolix/estradiol/norethindrone acetate (Oriahnn) also had a reduced change from baseline in bone mineral density compared to elagolix (Orilissa). Elaris UF-1 had similar rates of discontinuation due to adverse events

across all treatment arms; however, in Elaris UF-2, elagolix (Orilissa) had a discontinuation rate of 12.6% compared to 8.5% and 5.3% for elagolix/estradiol/norethindrone acetate (Oriahnn) and placebo, respectively. Elaris UF-EXTEND had lower rates of adverse events in the final six months compared to Elaris UF-1 and UF-2.

- The FDA has indicated that use of Oriahnn should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

XII. **Relugolix/estradiol/norethindrone (Myfembree)** was evaluated in the setting of heavy menstrual bleeding associated with uterine fibroids (leiomyoma) and moderate to severe pain associated with endometriosis.

- **Uterine Fibroids**: Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two Phase 3, double-blind, randomized, placebo-controlled trials over 24 weeks (LIBERTY 1 and LIBERTY 2). Therapy was evaluated in premenopausal women with heavy menstrual bleeding and diagnosis of uterine fibroids, confirmed via ultrasonography. Patients with osteoporosis or osteopenia were excluded.
- Primary outcome: percentage of participants with treatment response (blood loss volume < 80 mL and ≥ 50% reduction in volume). Secondary outcomes: proportion of patients reaching amenorrhea, change in blood loss volume, pain, distress from bleeding and pelvic discomfort, and participants that had a change in hemoglobin of 2 g/dL or more in those that had anemia at baseline. These outcomes were statistically and clinically significant over placebo. In clinical trials, relugolix/estradiol/norethindrone (Myfembree) did not reduce uterine fibroid volume.
- Relugolix was also evaluated as monotherapy in a randomized, blinded, non-inferiority (NI) trial vs. leuprorelin (Lupron). Relugolix showed to be NI to leuprorelin (Lupron) in the following outcomes: blood loss, amenorrhea, uterine volume, fibroid volume, hemoglobin improvement, pain, and quality of life. Estrogenic AE and decrease in BMD were notable; thus, the manufacturer is pursuing combination therapy with estradiol and norethindrone to mitigate these concerns. A limitation of the trial is the majority of patients received leuprorelin (Lupron) 1.88 mg, rather than the standard U.S. dose of 3.75 mg. Comparative safety and efficacy data to the 3.75 mg dose of leuprorelin (Lupron) is currently unknown.
- **Endometriosis:** Relugolix/estradiol/norethindrone (Myfembree) was evaluated in two replicate, phase 3, randomized, double-blind, placebo-controlled trial over 24 weeks (SPIRIT 1 and SPIRIT 2). Therapy was evaluated in pre-menopausal women aged 18 – 50 years with moderate to very severe dysmenorrhea and non-menstrual pelvic pain associated with endometriosis. Patients were excluded from the trial if they had a history of Z-score consistent with osteoporosis or osteopenia.
- The co-primary outcomes were the proportion of responders based on dysmenorrhea NRS score and non-menstrual pelvic pain (NMPP) NRS score at the end of treatment. In

both trials, relugolix/estradiol/norethindrone (Myfembree) demonstrated a statistically significant benefit in dysmenorrhea and NMPP compared to placebo. In SPIRIT 1, 75% of patients in the relugolix-CT group and 27% of patients in the placebo group were considered dysmenorrhea responders (95% CI 39.3-56.0; p<0.0001) while 59% of patients in the relugolix-CT group and 40% of patients in the placebo group were considered NMPP responders (95% CI 9.5-28.2; p<0.0001). In SPIRIT 2, 75% of patients in the relugolix-CT group and 30% of patients in the placebo group were considered dysmenorrhea responders (95% CI 36.2-53.5; p<0.0001) while 66% of patients in the relugolix-CT group and 43% of patients in the placebo group were considered NMPP responders (95% CI 14.0-32.8; p<0.0001).

- An extension trial (SPIRIT LTE) was conducted to assess the long-term efficacy and safety of relugolix with estradiol/norethindrone (relugolix-CT) for the treatment of moderate to severe pain associated with endometriosis up to 104 weeks. Participants were required to have completed 24 weeks of participation in either SPIRIT 1 or SPIRIT 2; all eligible patients were assigned to receive relugolix-CT during the 80-week, open-label treatment period. SPIRIT LTE used the same co-primary endpoints as the SPIRIT 1 and SPIRIT 2 trials. For the co-primary endpoint of dysmenorrhea responders, at the end of 104 weeks of treatment, 84.8% and 83.0% of patients in the relugolix-CT and delayed relugolix-CT groups, respectively were considered dysmenorrhea responders; at the end of 80 weeks of treatment, 80.4% of patients who initially received placebo were considered dysmenorrhea responders. For the co-primary endpoint of NMPP responders, 75.8% of patients in the relugolix-CT group and 71.7% of patients in the delayed relugolix-CT group were considered NMPP responders; in patients initially treated with placebo, 73.1% were considered NMPP responders at week 52. No new safety signals were identified during the long-term extension period.

XIII. In both the LIBERTY and SPIRIT trials, rate of overall AEs was consistent for placebo and active therapy. No deaths occurred in the trials and serious AEs were rare. In the LIBERTY trials, there were a few cases of ankle fracture in those that received relugolix/estradiol/norethindrone (Myfembree). At week 24 the BMD at lumbar spine and total hip were similar between groups. AE leading to treatment discontinuation occurred in 4-11% of patients. Common AE included the following: hot flash (6-11% vs. 4-8% for placebo) and hypertension (5% vs. 0% for placebo). Other AEs that occurred in ≥ 5% of patients included headache, arthralgia, cough, nausea, URI, nasopharyngitis, fatigue, and anemia. Long term safety is currently unknown but will be better understood with results from long-term safety extension trials. The FDA has indicated that use of Myfembree should be limited to 24 months due to the risk of continued bone loss with use, which may not be reversible.

XIV. Elagolix (Orilissa), elagolix/estradiol/norethindrone acetate (Oriahnn), and relugolix/estradiol/norethindrone (Myfembree) are contraindicated in pregnant patients due to

an increased risk of early pregnancy loss.

Investigational or Not Medically Necessary Uses

I. Elagolix and/or relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Polycystic ovary syndrome
   B. Fertility treatment

References

1. Orilissa [Prescribing Information]. North Chicago, IL: AbbVie Inc.; February 2021.
2. Oriahnn [Prescribing Information]. North Chicago, IL: AbbVie Inc.; August 2021.
3. Myfembree [Prescribing Information]. Patheaon Inc. Mississauga, Ontario, Canada. Myovant Sciences, Brisband, CA. September 2022.
4. UpToDate, Inc. Endometriosis: Treatment of pelvic pain. UpToDate [database online]. Waltham, MA. Updated July 29, 2019.
5. UpToDate, Inc. Clinical manifestations, diagnosis, and evaluation of osteoporosis in postmenopausal women. UpToDate [database online]. Waltham, MA. Updated July 11, 2019.
6. Taylor HS, Giudice LC, Lessey BA et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. *N Engl J Med*. 2017;377:28-40. doi: 10.1056/NEJMoa1700089.
7. UpToDate, Inc. Overview of treatment of uterine leiomyomas (fibroids). UpToDate [database online]. Waltham, MA. Updated November 11, 2019.
8. Lupron Depot [Prescribing Information]. Abbvie Inc. Chicago, IL. January 2019.
9. Gillispie V, Muneyyirci-Delale O, Kim J, Liu R, et al. Up to 12 months of efficacy and safety of elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroids. Presented at the American Association of Gynecologic Laparoscopists, November 9-13, 2019; Vancouver, Canada.
10. Schlaff W, Al-Hendy A, Barnhart K, et al. Elagolix Reduced Heavy Menstrual Bleeding with Uterine Fibroids: Primary, 6-month, Phase 3 Results. Presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists, May 3-6, 2019; Nashville, Tennessee, USA.
11. Bradley L, Feinberg E, Liu R, et al. Elagolix Treatment in Women with Uterine Fibroids: Secondary, 6-Month, Phase 3 Efficacy Results. Presented at the 2019 American College of Obstetricians and Gynecologists Annual Clinical and Scientific Meeting, May 3-6, 2019; Nashville, Tennessee, USA.
12. Giudice LC, As-Sanie S, Ferreira JCA, et al. Once daily oral relugolix combination therapy versus placebo in patients with endometriosis-associated pain: two replicate phase 3, randomized, double-blind, studies (SPIRIT 1 and 2). Lancet 2022; 399: 2267-79.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
relugolix (Orgovyx™)	Prostate cancer

Gonadotropin-releasing hormone (GnRH)	Endometriosis, Central Precocious Puberty (CPP), Advanced Prostate Cancer, Uterine leiomyoma (fibroids), Advanced breast cancer in premenopausal women, Reduction of endometrial thickness prior to endometrial ablation, Gender Dysphoria

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria updated to include Myfembree for the indication uterine fibroids and moderate to severe pain with endometriosis; Changed policy name to 'GnRH Antagonists in Gynecologic Conditions'.	11/2022
Criteria updated to require specialist prescriber, removal of check on pregnancy status and menopausal status, and addition of assessment for prior use of GnRH antagonist relugolix. Supporting evidence updated, and format of policy updated to follow new standards. Experimental and investigational section added.	05/2021
Removed criteria: "Must be used in combination with an estradiol/norethindrone acetate product (Activella, Combipatch, Mimvey Lo, etc.)" from the indication heavy menstrual bleeding associated with uterine fibroids	12/2020
Added criteria for treatment of heavy menstrual bleeding associated with uterine fibroids, added requirements for premenopause and confirmation member is not pregnant. Also added NSAIDS as an option for trial and failure for pain associated with endometriosis.	12/2019
Transition from criteria to policy	09/2019
Criteria created	10/2018