BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

MYFEMBREE® (relugolix, estradiol, norethindrone acetate) oral
ORIAHNN® (elagolix, estradiol, norethindrone acetate) oral
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for therapy:** Myfembree (relugolix, estradiol, norethindrone acetate), Oriahnn (elagolix, estradiol, and norethindrone acetate), and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Gynecologist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. **For Myfembree**, **ONE** of the following:

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i. Heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal woman
ii. Moderate to severe pain associated with endometriosis in premenopausal woman

b. **For Oriahnn**: Heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal woman

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate:
   a. Bone Mineral Density (BMD) assessment by dual-energy X-ray absorptiometry (DXA)
   b. Negative pregnancy test in a woman of childbearing potential

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. **ONE** of the following:
   a. **For Heavy menstrual bleeding associated with uterine leiomyomas (fibroids)** in premenopausal woman: Documented failure, contraindication per FDA label, intolerance, or is not a candidate for **ONE** of the following:
      i. Estrogen-progestin contraceptive (e.g., oral, vaginal ring or transdermal patch)
      ii. Progestin-only contraceptive (e.g., norethindrone)
      iii. Progestin-releasing intrauterine device
      iv. Tranexamic acid
   b. **For moderate to severe pain associated with endometriosis** in premenopausal woman: Documented failure, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
      i. **ONE** non-steroidal anti-inflammatory agent such as ibuprofen, indomethacin, naproxen, meloxicam, and others
      ii. **ONE** hormonal product such as oral estrogen-progestin contraceptive or progestin (oral or depot (e.g., medroxyprogesterone or norethindrone acetate))

7. There are **NO** FDA-label contraindications such as:
   a. High risk of arterial, venous thrombotic, or thromboembolic disorder such as:
      i. Over 35 years of age who smoke and known to have:
         1. Current or history of deep vein thrombosis or pulmonary embolism
         2. Vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral artery disease, peripheral vascular disease)
         3. Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
         4. Inherited or acquired hypercoagulopathies
         5. Uncontrolled hypertension
         6. Headaches with focal neurological symptoms or migraine headaches with aura if over 35 years of age
   b. Pregnancy
   c. Known osteoporosis

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d. Current or history of breast cancer or other hormone-sensitive malignancies
e. Known hepatic impairment or disease
f. Undiagnosed abnormal uterine bleeding
g. **Additional for Oriahnn only**: Organic anion transporting polypeptide (OATP)1B1 inhibitors (e.g., cyclosporine, gemfibrozil), rifampin, and strong CYP3A inhibitors

8. **For Myfembree only:** Individual is not using combined P-gp and strong CYP3A inducers such as carbamazepine, nefazodone, phenobarbital, phenytoin, prazosin, rifampicin, St. John's wort, tenofovir, tipranavir, trazodone, and others

9. Individual has not previously received 24 months or longer of therapy with Myfembree or Oriahnn either alone or sequentially

Approval duration:
Up to 24 months maximum due to the risk of continued bone loss which may not be reversible
Calculation of duration will consider any previous use so that total 24 months use will be allowed

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Myfembree is a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin. It is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women and for the management of moderate to severe pain associated with endometriosis premenopausal women. Myfembree use should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

Oriahnn is a combination of elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin. It is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Oriahnn use should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

The combination of a GnRH antagonist with an estrogen and progestin is considered “add-back” therapy which offsets the hypoestrogenic effects of the GnRH antagonist, minimizing hot flushes, increases in serum lipid levels and loss of bone mineral density.

Uterine leiomyomas are noncancerous tumors that may arise in females of reproductive age. They are common in premenopausal women but are largely asymptomatic and often go undiagnosed. It is estimated that 25% of women with leiomyomas have symptoms clinically significant enough to require intervention. The most common

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presenting symptoms include prolonged or heavy bleeding, with or without anemia and menstrual cramping. Other bulk-related symptoms arise from an enlarged uterus, which may include feelings of fullness similar to pregnancy, urinary frequency, constipation, pressure, and pain. Additionally, leiomyomas may cause reproductive dysfunction.

Treatment of symptomatic uterine leiomyomas includes expectant (monitoring), medical, interventional, and surgical therapies. Medical treatments primarily address bleeding symptoms and procedural and surgical approaches decrease uterine or fibroid mass. Medical treatment options that address bleeding symptoms are GnRH antagonists, levonorgestrel-releasing intrauterine devices (IUDs), contraceptive steroids and tranexamic acid. GnRH agonists reduce both bleeding and leiomyoma size but are primarily used as a bridge to a procedure or surgery due to their risk of blood loss and regrowth of fibroids after drug cessation.

Endometriosis is an estrogen-dependent, benign, inflammatory disease that can affect a woman during their premenarcheal, reproductive, and postmenopausal hormonal stages. Ectopic endometrial tissue and inflammation may cause dysmenorrhea, dyspareunia, chronic pelvic pain, pelvic tenderness, pelvic induration, infertility and/or an ovarian mass. Less common symptoms include bowel and bladder dysfunction (e.g., dyschezia and dysuria), abnormal uterine bleeding, low back pain, or chronic fatigue. For some, the disease is asymptomatic and is an incidental finding at the time of surgery or imaging done for other indications.

For women with mild to moderate pain, nonsteroidal anti-inflammatory drugs (NSAIDs), continuous hormonal contraceptives (combined estrogen-progestin oral contraceptive), or gonadotropin-releasing hormone (GnRH) agonist can be used for the initial treatment of pain in women with suspected endometriosis. For women with chronic endometriosis-related pelvic pain unresponsive to oral contraceptives or progestins, GnRH agonist may be used. GnRH antagonists are a newer therapeutic agent for moderate to severe pain related to endometriosis.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Myfembree (relugolix, estradiol, norethindrone) product information, revised by Sumitomo Pharma America. 04-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 06, 2024.

Oriahnn (elagolix, estradiol, norethindrone) product information, revised by AbbVie, Inc. 06-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed June 06, 2024.

Stewart EA. Uterine fibroids (leiomyomas): Treatment Overview. In: UpToDate, Barbierie RL, Chakrabarti A (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated June 14, 2024. Accessed July 24, 2024.

Stewart EA, Laughlin-Tommaso SK. Uterine fibroids (leiomyomas): Epidemiology, clinical features, diagnosis, and natural history. In: UpToDate, Barbierie RL, Levine D, Chakrabarti A (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated June 16, 2024. Accessed July 24, 2024.

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Schenken RS. Endometriosis: Pathogenesis, epidemiology, and clinical impact. In: UpToDate, Barbieri RL, Eckler K (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated July 22, 2024. Accessed July 24, 2024.

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Hornstein MD, Gibbons WE. Endometriosis: Long-term treatment gonadotropin-releasing hormone agonists. In: UpToDate, Barbieri RL, Eckler K (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through June 2024. Topic last updated March 21, 2023. Accessed July 24, 2024.

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