BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

MYFEMBREE® (relugolix, estradiol hemihydrate, norethindrone acetate) oral tablet

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 precertification 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 initial therapy:** Myfembree (relugolix, estradiol hemihydrate, norethindrone acetate 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 heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women diagnosed by ultrasound.

  4. The 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. Documented failure, contraindication per FDA label, intolerance, or not a candidate to **BOTH** of the following:
   a. Hormone contraception (e.g., estrogen-progestin oral, vaginal ring or transdermal patch, or progestin-releasing intrauterine device)
   b. Tranexamic acid

6. There are **NO** FDA-label contraindications, such as:
   a. High risk of arterial, venous thrombotic, or thromboembolic disorder (see Definition Section)
   b. Pregnancy
   c. Known osteoporosis
   d. Current or history of breast cancer or other hormone-sensitive malignancies
   e. Known hepatic impairment or disease
   f. Undiagnosed abnormal uterine bleeding

7. 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

8. Individual has not previously received 24 months or longer of any gonadotropin-releasing hormone (GnRH) antagonists (e.g., Myfembree, Oriahnn, Orilissa).

9. Will not be used with hormonal contraceptives or other GnRH antagonists (e.g., Oriahnn, Orilissa).

Initial approval duration: 12 months

- **Criteria for continuation of coverage (renewal request):** Myfembree (relugolix, estradiol hemihydrate, norethindrone acetate) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Gynecologist.

2. Individual's condition has responded defined as reduction of menstrual blood loss by at least 50%.

3. Individual has been adherent with the medication.

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use as follows:
   a. Contraindications as listed in the criteria for initial therapy section
   b. Significant adverse effect such as:
      i. Uncontrolled blood pressure
      ii. Gall bladder disease or jaundice or liver injury
      iii. Suicidal ideation, new or worsening depression, anxiety, or other serious mood changes
      iv. Arterial or venous thrombotic, cardiovascular, or cerebrovascular event
      v. Sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesion

5. 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

6. Individual has not previously received 24 months or longer of any GnRH antagonists (e.g., Myfembree, Oriahnn, Orilissa).

7. Will not be used with hormonal contraceptives or other GnRH antagonists (e.g., Oriahnn, Orilissa).

Renewal duration: 12 months
NOTE: Maximum total duration of approval is 24 months due to the risk of continued bone loss which may not be reversible

- 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:

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 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.

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. Myfembree 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.

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Definitions:

Examples of women with high risk of arterial, venous thrombotic, or thromboembolic disorders:

- Over 35 years of age who smoke
- Current or history of deep vein thrombosis or pulmonary embolism
- Vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral artery disease, peripheral vascular disease
- Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
- Inherited or acquired hypercoagulopathies
- Uncontrolled hypertension
- Headaches with focal neurological symptoms or migraine headaches with aura if over 35 years of age

Resources:

Myfembree (relugolix, estradiol hemihydrate, norethindrone) product information, revised by Myovant Sciences, Inc. 05-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 26, 2022.

Stewart EA. Uterine fibroids (leiomyomas): Treatment Overview. In: UpToDate, Barbierie RL, Chakrabarti A (Ed), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated on July 05, 2022. Accessed July 26, 2022.

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. Topic last updated on May 17, 2022. Accessed July 26, 2022.