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/or 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.

Medical Necessity Requirements for MYFEMBREE (relugolix, estradiol, norethindrone acetate) oral

Criteria for Initial Therapy:

Prescriber Qualifications
- Prescribed by a Gynecologist or in consultation with a Gynecologist

Indication
- Heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal woman

- Moderate to severe pain associated with endometriosis in premenopausal woman

Age Requirement
- 18 years or older

Baseline Clinical Evaluation
- Bone Mineral Density assessment by dual energy X ray absorptiometry
- Negative pregnancy test in a woman of childbearing potential

Alternative Therapies
- Heavy menstrual bleeding associated with uterine leiomyomas (fibroids)
  - Failure, contraindication, intolerance, or not a candidate for **ONE** of the following:
    1. Estrogen progestin contraceptive (oral, vaginal ring, or transdermal patch)
    2. Progestin only contraceptive (e.g., norethindrone)
    3. Progestin releasing intrauterine device
    4. Tranexamic acid
- Moderate to severe pain associated with endometriosis
  - Failure, contraindication, intolerance, or not a candidate for **BOTH** of the following:
    1. **ONE** non steroidal anti inflammatory agent (e.g., ibuprofen, indomethacin, naproxen, meloxicam, etc.)
    2. **ONE** hormonal product (oral estrogen progestin contraceptive or progestin oral or depot such as medroxyprogesterone or norethindrone acetate)

Brand Specific Criteria
- Have failure, contraindication or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the U.S. Food and Drug Administration (FDA) (see Definitions section)

Safety
- No concomitant use of combined P glycoprotein and strong CYP3A inducers such as carbamazepine, nefazodone, phenobarbital, phenytoin, prazosin, rifampicin, St. John's wort, tenofovir, tipranavir, trazodone, etc.
- Does not have any of the following contraindications such as
  - High risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include women over 35 years of age who smoke and women who are 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 rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease, atrial fibrillation)
    4. Inherited or acquired hypercoagulopathies

5. Uncontrolled hypertension
6. Headaches with focal neurological symptoms or migraine with aura if over 35 years of age

- Pregnancy
- Known osteoporosis
- Current or history of breast cancer or other hormone sensitive malignancies
- Known hepatic impairment or disease
- Undiagnosed abnormal uterine bleeding

- Has not previously received 24 months or longer of therapy with Myfembree, Oriahnn, or Orilissa either alone or sequentially

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (Bone Mineral Density, pregnancy test)
  - Supporting clinical documentation

Initial Therapy Criteria Approval Duration

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

Medical Necessity Requirements for ORIAHNN (elagolix, estradiol, norethindrone acetate)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by a Gynecologist or in consultation with a Gynecologist

Indication

- Heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in a premenopausal woman

Age Requirement

- 18 years of age or older

Baseline Clinical Evaluation

- Bone Mineral Density assessment by dual energy X ray absorptiometry
- Negative pregnancy test in a woman of childbearing potential

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Alternative Therapies

- Failure, contraindication per FDA label, intolerance, or not a candidate for **ONE** of the following:
  - Estrogen progestin contraceptive (oral, vaginal ring, or transdermal patch)
  - Progestin only contraceptive (e.g., norethindrone)
  - Progestin releasing intrauterine device
  - Tranexamic acid

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- Does not have any of the following contraindications such as
  - High risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include:
    1. Women over 35 years of age who smoke and women who are known to have over 35 years of age who smoke and known to have):r
    2. Current or history of deep vein thrombosis or pulmonary embolism
    3. Vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral artery disease, peripheral vascular disease)
    4. Thrombogenic valvular or rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease, atrial fibrillation)
    5. Inherited or acquired hypercoagulopathies
    6. Uncontrolled hypertension
    7. Headaches with focal neurological symptoms or migraine with aura if over 35 years of age
  - Pregnancy
  - Known osteoporosis
  - Current or history of breast cancer or other hormone sensitive malignancies
  - Known hepatic impairment or disease
  - Undiagnosed abnormal uterine bleeding
  - Concomitant use with organic anion transporting polypeptide (OATP)1B1 inhibitors (e.g., cyclosporine, gemfibrozil), rifampin, and strong CYP3A inhibitors
- Has not previously received 24 months or longer of therapy with Myfembree, Oriahnn, or Orilissa either alone or sequentially

Documentation Requirements

- A completed request form must be submitted, including:
  - Chart notes
  - Lab results (Bone Mineral Density, pregnancy test)
  - Supporting clinical documentation

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Initial Therapy Approval Duration

- Up to a total of 24 months of therapy (considering any previous use of Myfembree, Oriahnn, or Orilissa) due to the risk of continued bone loss which may not be reversible, OR end of plan year

Criteria for Continuation of Therapy (renewal therapy):

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualifications

- Continues to be managed by a physician who specializes in treating uterine leiomyomas, **or** is in consultation with a gynecologist

Clinical Response

- Ongoing use is for the same approved indication for which initial therapy was granted: heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in a premenopausal woman
- Treating provider documents that continued Oriahnn therapy is medically necessary for control of heavy menstrual bleeding.

Adherence

- Adherence to the prescribed therapy regimen has been documented

Alternative Therapies

- Documented failure, contraindication per FDA label, intolerance, or not a candidate for **ONE** of the following:
  - Estrogen progestin contraceptive (oral contraceptive, vaginal ring, or transdermal patch).
  - Progestin only contraceptive such as norethindrone.
  - Progestin releasing intrauterine device
  - Tranexamic acid

Brand Specific Criteria

- Have failure, contraindication or intolerance with **THREE** generic equivalents (if available) for at least three months each. **Note**: Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- No new or worsened conditions that would create a United States Food and Drug Administration label contraindication for Oriahnn, including
  - New high risk arterial, venous thrombotic, or thromboembolic condition
  - New pregnancy
  - Development of osteoporosis

  - New diagnosis of breast cancer or other hormone sensitive malignancy
  - New hepatic impairment or hepatic disease
  - New unexplained abnormal uterine bleeding.
- No concomitant use of organic anion transporting polypeptide 1B1 inhibitors, rifampin, or strong cytochrome P450 3A inhibitors while continuing therapy
- Has not previously received 24 months or longer of therapy with Myfembree, Oriahnn, or Orilissa either alone or sequentially

Documentation Requirements

- A completed continuation request form must be submitted, including:
  - Updated chart notes describing current symptoms and response to treatment
  - Supporting clinical documentation showing that the indication remains appropriate for therapy
  - Any updated lab or diagnostic data that confirm safe use, including bone mineral density evaluations as clinically appropriate

Continuation Therapy Approval Duration

- Up to the remaining portion of the overall 24 month maximum treatment duration (including all prior use of Myfembree, Oriahnn, and Orilissa), OR end of plan year

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Criteria for Off-Label Use Requests:

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.

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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 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. 07-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 25, 2025.

Oriahnn (elagolix, estradiol, norethindrone) product information, revised by AbbVie, Inc. 06-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 25, 2025.

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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 May 2025. Topic last updated August 26, 2024. Accessed June 16, 2025.

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 May 2025. Topic last updated June 16, 2024. Accessed June 16, 2025.

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 May 2025. Topic last updated December 03, 2024. Accessed June 16, 2025.

Schenken RS. Endometriosis: Treatment of pelvic pain. In: UpToDate, Barbieri RL, Eckler K (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated May 14, 2025. Accessed June 16, 2025.

Hornstein MD. Endometriosis: Long-term treatment with gonadotropin-releasing hormone agonists. In: UpToDate, Barbieri RL, Eckler K (Eds), UpToDate, Waltham, MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through May 2025. Topic last updated March 21, 2023. Accessed June 16, 2025.