Novel Medications for the Treatment of Uterine Fibroids

Policy # 00730
Original Effective Date: 02/08/2021
Current Effective Date: 07/01/2025

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Orilissa™ (elagolix) is addressed separately in medical policy 00659.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider Oriahnn™‡ (elagolix/estradiol/norethindrone) or Myfembree®‡ (relugolix/estradiol/norethindrone) to be **eligible for coverage**** when the patient selection criteria are met.

Patient Selection Criteria

Coverage eligibility for Oriahnn (elagolix/estradiol/norethindrone) or Myfembree (relugolix/estradiol/norethindrone) will be considered when the following criteria are met for the requested drug:

- Requested drug is Oriahnn:
  - Patient has a diagnosis of heavy menstrual bleeding associated with uterine leiomyomas (fibroids); AND
  - Patient is premenopausal; AND
  - Oriahnn and/or Myfembree will not be used for longer than 24 months (alone or in combination).
- Requested drug is Myfembree:
  - Patient has a diagnosis of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) and ALL of the following:
    - Patient is premenopausal; AND
    - Oriahnn and/or Myfembree will not be used for longer than 24 months (alone or in combination); OR
  - Patient has a diagnosis of endometriosis and ALL of the following
    - Patient is premenopausal; AND

- Patient is not pregnant; AND
- Patient is greater than or equal to 18 years of age; AND
- Oriahnn and/or Myfembree will not be used for longer than 24 months (alone or in combination).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of Oriahnn (elagolix/estradiol/norethindrone) or Myfembree (relugolix/estradiol/norethindrone) when patient selection criteria are not met to be **investigational.***

Background/Overview

Oriahnn contains elagolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist that binds to GnRH receptors in the pituitary gland and results in suppression of luteinizing hormone (LH) and follicle stimulating hormone (FSH). Myfembree contains relugolix which is also a GnRH receptor antagonist. Both of these compounds decrease the blood concentrations of estradiol and progesterone. Oriahnn and Myfembree also contain estradiol and norethindrone which are considered "add back" therapy to attenuate the side effects of GnRH therapy. Both products are indicated to manage heavy menstrual bleeding associated with uterine fibroids in premenopausal women and Myfembree has the additional indication for the management of moderate to severe pain associated with endometriosis in premenopausal women. The recommended dose of Oriahnn is one capsule in the morning (containing elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg) and one capsule in the evening (containing elagolix 300 mg). Myfembree is dosed once daily for both indications with one capsule taken at approximately the same time each day. Similar to other estrogen-containing products, these products have boxed warnings for an increased risk of thrombotic or thromboembolic disorders and are contraindicated in women with a current history of thrombotic or thromboembolic disorders or at increased risk for these events. Additionally, the use of these products (alone or in combination with each other) should be limited to 24 months due to the risk of continued bone loss, which may not be reversible.

Uterine leiomyomas (fibroids) are benign tumors that are thought to affect up to 80% of women by the age of 50 years. In most cases, these fibroids are asymptomatic, but they can cause the symptoms of abnormal (heavy) uterine bleeding and pelvic pain or pressure. The clinical diagnosis of uterine fibroids is typically made based upon pelvic examination and pelvic ultrasound. Surgical interventions including hysterectomy and myomectomy still represent the main strategies for uterine fibroid management. Medical management for symptomatic fibroids includes combination oral contraceptives, progestins, and GnRH agonists. The goal of medical therapy is to help with symptomatic bleeding and/or pain.

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Endometriosis is a condition where the tissues similar to the lining of the uterus (or endometrium) migrate outside of the womb to other body sites. The migrated tissues are generally found in the pelvic cavity (e.g., peritoneum, uterosacral ligaments, rectal-vaginal septum, or any spaces between the bladder, uterus, vagina, and rectum) and can attach to any of the female reproductive organs. The migrated tissue is less commonly found outside the pelvic cavity or in the intestines, colon, appendix, or rectum. Endometriosis impacts up to 10% of patients of reproductive age in the United States. Many women are not diagnosed and therefore, not treated. The most common symptom of endometriosis is pelvic pain, which often correlates to the menstrual cycle. Symptoms can range from minimal to severely debilitating. May women with endometriosis also experience dyspareunia and infertility. The definitive diagnosis of endometriosis can only be made by histology of lesions removed at surgery (laparoscopy), although empiric therapy is commonly used in the course of evaluating the condition. There is no cure for the condition, but many treatments are available to help relieve symptoms associated with endometriosis. Non-FDA approved therapies which are commonly used include: non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, and some contraceptives. FDA-approved products for the management of endometriosis include GnRH agonists (Lupron Depot [leuprolide acetate], Zoladex®‡ [goserelin acetate], Synarel®‡ [nafarelin acetate]), synthetic androgen therapy (danazol capsules), and the GnRH antagonists Orilissa™‡ (elagolix) and Myfembree. Additionally, surgery can be performed to reduce endometriosis-associated pain by removing all visible endometriosis and any associated adhesions. There is a significant rate of pain recurrence with medical management and conservative surgical treatment.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Both Oriahnn and Myfembree are approved for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Myfembree gained an additional indication in August 2022 for the management of moderate to severe pain associated with endometriosis in premenopausal women.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Oriahnn
The efficacy of Oriahnn in the management of heavy menstrual bleeding associated with uterine fibroids was demonstrated in two identical randomized, double-blind, placebo-controlled studies (Study UF-1 and Study UF-2) in which 790 premenopausal women with heavy menstrual bleeding received Oriahnn or placebo for 6 months. Heavy menstrual bleeding at baseline was defined as

having at least 2 menstrual cycles with greater than 80 mL of menstrual blood loss (MBL) as assessed by alkaline hematin (AH) method (an objective, validated measure to quantify MBL volume on sanitary products).

The primary endpoint in both studies was the proportion of responders, defined as women who achieved both 1) MBL volume less than 80 mL at the final month and 2) 50% or greater reduction in MBL volume from baseline to the final month. The final month was defined as the last 29 days before and including the last treatment visit date or last dose date. A higher proportion of Oriahnn-treated women were responders compared to placebo-treated women. In Study UF-1, 68.5% met the primary endpoint in the Oriahnn group vs 8.7% in the placebo group ($p<0.001$). In Study UF-2, 76.5% met the primary endpoint in the Oriahnn group vs 10.5% in the placebo group ($p<0.001$).

Myfembree- Uterine Fibroids
The efficacy and safety of Myfembree were evaluated in two replicate, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal women with heavy menstrual bleeding associated with uterine fibroids in Study L1 and Study L2. For study inclusion, women had to have uterine fibroids confirmed by ultrasound examination in which at least one fibroid met at least one of the following criteria:

- Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter $\geq$ 2 cm, or
- Multiple small fibroids with a total uterine volume of $\geq$ 130 cm^3.

Women also had to have MBL volume of $\geq$ 80 mL per cycle for 2 menstrual cycles or $\geq$ 160 mL during one cycle quantified by the alkaline hematin method. Women with hemoglobin < 8 g/dL were excluded from the study. Iron therapy was required for women with hemoglobin $\leq$ 10 g/dL. Women were allowed, but not required, to take calcium and vitamin D during the study.

In both studies, women were randomized 1:1:1 to receive a once daily relugolix 40 mg tablet plus an over encapsulated tablet of estradiol 1 mg and norethindrone 0.5 mg for 24 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for 12 weeks followed by Myfembree for 12 weeks. Treatment was initiated within the first seven days after the onset of menses.

The primary endpoint was the proportion of women in the Myfembree group compared with women in the placebo group who achieved MBL volume of < 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by the alkaline hematin method. In both studies, a statistically higher proportion of women treated with Myfembree achieved the primary endpoint with 72.1% achieving it in study L1 compared to 16.8% in the placebo arm and 71.2% achieving it in study L2 compared to 14.7% in the placebo arm.

Myfembree- Endometriosis
The efficacy of Myfembree was assessed in two 24-week, multinational, randomized, double-blind, placebo-controlled studies in pre-menopausal women with moderate to severe pain associated with endometriosis in Study S1 and Study S2. In both studies, women were randomized 1:1:1 to receive

once daily treatment with Myfembree for 24 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for 12 weeks followed by Myfembree for 12 weeks. For study inclusion, women had to have endometriosis confirmed by direct visualization during surgery and/or histology in addition to pain associated with endometriosis during a placebo run-in period. Dysmenorrhea and non-menstrual pelvic pain were assessed daily using an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (pain as bad as you can imagine). Specifically, women had to have pain that met the following criteria:

- Dysmenorrhea score $\geq$ 4.0 on at least 2 days AND
- Mean non-menstrual pelvic pain score $\geq$ 2.5 OR
- Mean non-menstrual pelvic pain score $\geq$ 1.25 AND non-menstrual pelvic pain score $\geq$ 5.0 on at least 4 days

Studies S1 and S2 each had two co-primary endpoints. The first was a responder analysis where a responder was defined as a woman who achieved a reduction from baseline in dysmenorrhea NRS of at least 2.8 points over the last 35 days of treatment, without an increase in analgesic use. The second co-primary endpoint was a responder analysis where a responder was defined as a woman who achieved a reduction from baseline in non-menstrual pelvic pain NRS score of at least 2.1 points over the last 35 days of treatment, without an increase in analgesic use for pain associated with endometriosis.

In Study S1, a total of 424 women were included in the efficacy population (212 received Myfembree and 212 received placebo). At Week 24, 74.5% of the Myfembree group were considered responders for the dysmenorrhea endpoint compared to 26.9% in the placebo group ($p < 0.0001$). For the non-menstrual pelvic pain endpoint, 58.5% of the Myfembree group were responders compared to 39.6% of the placebo group ($p<0.0001$).

In Study S2, a total of 405 women were included in the efficacy population (205 received Myfembree; 200 received placebo). At Week 24, 75.1% of the Myfembree group were considered responders for the dysmenorrhea endpoint compared to 30.5% in the placebo group ($p < 0.0001$). For the non-menstrual pelvic pain endpoint, 65.9% of the Myfembree group were responders compared to 42.5% of the placebo group ($p < 0.0001$).

References

1. Oriahnn [package insert]. AbbVie Inc. North Chicago, IL. Updated May 2020.
2. Oriahnn Drug Evaluation. Express Scripts. Updated June 2020.
3. Myfembree [package insert]. Myovant Sciences, Inc. Brisbane, CA. Updated February 2023.

Policy History

Original Effective Date: 02/08/2021
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01/07/2021 Medical Policy Committee review
01/13/2021 Medical Policy Implementation Committee approval. New policy.

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01/06/2022	Medical Policy Committee review
01/12/2022	Medical Policy Implementation Committee approval. No change to coverage.
03/03/2022	Medical Policy Committee review
03/09/2022	Medical Policy Implementation Committee approval. Added new product, Myfembree, to policy with relevant criteria and background information. Changed title from "Oriahnn (elagolix/estradiol/norethindrone)" to "Novel Medications for the Treatment of Uterine Fibroids."
03/02/2023	Medical Policy Committee review
03/08/2023	Medical Policy Implementation Committee approval. Updated criteria and background information to reflect new indication for Myfembree for endometriosis.
03/07/2024	Medical Policy Committee review
03/13/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/06/2025	Medical Policy Committee review
03/12/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/05/2025	Medical Policy Committee review
06/11/2025	Medical Policy Implementation Committee approval. Removed criteria requiring trial and failure of other agents.

Next Scheduled Review Date: 06/2026

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.