Oral Gonadotropin-Releasing Hormone Antagonists

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

The intent of the Oral Gonadotropin Releasing Hormone Antagonists policy is to ensure appropriate selection of patients for therapy based on product labeling, FDA guidance, standards of medical practice, evidence-based drug information, published clinical guidelines, and/or clinical studies.

FDA-Approved Indications

Oriahnn (elagolix/estradiol/norethindrone and elagolix) & Myfembree (relugolix/estradiol/norethindrone) are indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (i.e., fibroids) in premenopausal women.

Orilissa (elagolix) and Myfembree (relugolix/estradiol/norethindrone) are indicated for the management of moderate to severe pain associated with endometriosis.

Limitations of Use

Use of Orilissa (elagolix), Oriahnn (elagolix/estradiol/norethindrone and elagolix), and Myfembree (relugolix/estradiol/norethindrone) should be limited to 24 months due to the risk of continued bone loss, which may not be reversible. Bone mineral density (BMD) loss is greater with increasing duration of use and may not be completely reversible after stopping treatment. It is recommended to limit the duration of these agents to reduce the extent of bone loss in patients. The use of higher doses limits use even farther. Therefore, the recommended duration of therapy for Orilissa is only 6 months for patients taking the higher dose of 200 mg twice daily.

POLICY

Documentation Required

Medical records documenting medication history and past medical history

Prescriber requirement
For initial requests: the requested medication is prescribed by or in consultation with an obstetrician-gynecologist

Criteria for Initial Approval

I. Orilissa (elagolix) may be considered **medically necessary** for when the following criteria are met:
   - The patient is 18 years of age or older
   - The patient has the diagnosis of moderate to severe pain associated with endometriosis
   - The patient is not pregnant
   - The patient has not already received ≥24 months of treatment with elagolix-containing products (e.g., Oriahnn, Orilissa) and/or a relugolix-containing product (Myfembree) OR the patient has not already received ≥ 6 months of treatment with Orilissa 200mg twice daily
   - The patient has tried and had an inadequate treatment response or intolerance to a 3-month trial of at least one hormonal contraceptive (e.g., combined oral contraceptives, depot medroxyprogesterone, norethindrone acetate, etonogestrel implant, etc.)
   - The patient does not have osteoporosis or severe hepatic impairment (Child-Pugh Class C)
   - The patient is not concomitantly taking an OATP 1B1 inhibitor (i.e. gemfibrozil, cyclosporine, ritonavir, rifampin)
   - The patient meets ONE of the following:
     - The request is for 150 mg once daily for a maximum of 24 months and the patient has mild (Child-Pugh class A) or no hepatic impairment
     - The request is for 200 mg twice daily for a maximum of 6 months, the patient has mild (Child-Pugh class A) or no hepatic impairment, and dyspareunia
     - The request is for 150mg once daily for a maximum of 6 months and the patient has moderate hepatic impairment (Child-Pugh class B)

   Initial approval will be for up to **6 months.**

II. Oriahnn may be considered **medically necessary** for the management of heavy menstrual bleeding associated with uterine leiomyomas (i.e., fibroids) in premenopausal women when ALL of the following criteria are met:
   - The patient has a diagnosis of heavy menstrual bleeding due to uterine leiomyomas (fibroids)
   - The patient has not already received ≥24 months of treatment with elagolix-containing products (e.g., Oriahnn, Orilissa) and/or a relugolix-containing product (e.g., Myfembree) OR the patient has not already received ≥ 6 months of treatment with Orilissa 200mg twice daily
   - The patient is premenopausal
   - The patient is not pregnant and does not have undiagnosed abnormal uterine bleeding
   - The patient tried and had an inadequate treatment response or intolerance to a 3-month trial of all of the following; OR has a documented clinical reason such as expected adverse reaction or contraindication that prevents them from trying the following medications; OR the member is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
     i. Tranexamic acid tablets
        AND
     ii. A hormonal contraceptive (e.g., combined oral contraceptives, depot medroxyprogesterone, norethindrone acetate, etonogestrel implant, etc.)
   - The patient does not have osteoporosis or any known hepatic impairment or disease
   - The patient does not have current or history of high-risk arterial, venous thrombotic, or thromboembolic disorders and is not at increased risk for these events (e.g., women >35 years of age who smoke, uncontrolled hypertension, etc.)

- The patient does not have current or history of breast cancer or other hormonally-sensitive malignancy
- The patient is not concomitantly taking an OATP 1B1 inhibitor (i.e., gemfibrozil, cyclosporine, ritonavir, rifampin)

Initial approval will be granted for **6 months.**

III. Myfembree may be considered **medically necessary** for the management of heavy menstrual bleeding associated with uterine leiomyomas (i.e., fibroids) in premenopausal women when ALL of the following criteria are met:
- The patient has a diagnosis of heavy menstrual bleeding due to uterine leiomyomas (fibroids)
- The patient has not already received ≥24 months of treatment with elagolix-containing products (e.g., Oriahnn, Orilissa) and/or a relugolix-containing product (Myfembree) OR the patient has not already received ≥ 6 months of treatment with Orilissa 200mg twice daily
- The patient is premenopausal
- The patient is not pregnant and does not have undiagnosed abnormal uterine bleeding
- The patient tried and had an inadequate treatment response or intolerance to a 3-month trial of all of the following; OR has a documented clinical reason such as expected adverse reaction or contraindication that prevents them from trying the following medications; OR the member is currently receiving treatment with the requested product through insurance (excludes obtainment as samples or via manufacturer's patient assistance programs) and experiencing a positive therapeutic outcome:
    i. Tranexamic acid tablets
    AND
    ii. A hormonal contraceptive (e.g., combined oral contraceptives, depot medroxyprogesterone, norethindrone acetate, etonogestrel implant, etc.)
- The patient does not have osteoporosis or any known hepatic impairment or disease
- The patient does not have current or history of high-risk arterial, venous thrombotic, or thromboembolic disorders and is not at increased risk for these events (e.g., women >35 years of age who smoke, uncontrolled hypertension, etc.)
- The patient does not have current or history of breast cancer or other hormonally-sensitive malignancy

Initial approval will be granted for **6 months.**

IV. Myfembree may be considered **medically necessary** for the management of moderate to severe pain associated with endometriosis in premenopausal women when ALL of the following criteria are met:
- The patient has a diagnosis of moderate to severe pain associated with endometriosis
- The patient has not already received ≥24 months of treatment with elagolix-containing products (e.g., Oriahnn, Orilissa) and/or a relugolix-containing product (Myfembree) OR the patient has not already received ≥ 6 months of treatment with Orilissa 200mg twice daily
- The patient is premenopausal
- The patient is not pregnant
- The patient has tried and had an inadequate treatment response or intolerance to a 3-month trial of at least one hormonal contraceptive (e.g., combined oral contraceptives, depot medroxyprogesterone, norethindrone acetate, etonogestrel implant, etc.)
- The patient does not have osteoporosis or any known hepatic impairment or disease
- The patient has not received the maximum recommended treatment course of 12 months of Lupron Depot or Lupaneta Pack OR 6 months of Synarel or Zoladex

- The patient does not have current or history of high-risk arterial, venous thrombotic, or thromboembolic disorders and is not at increased risk for these events (e.g., women >35 years of age who smoke, uncontrolled hypertension, etc.)
- The patient does not have current or history of breast cancer or other hormonally-sensitive malignancy

Initial approval will be granted for **6 months.**

Continuation of Therapy

I. Orilissa (elagolix) may be considered **medically necessary** for the continuation of treatment of moderate to severe pain associated with endometriosis when the following criteria are met:

- The request is for the continuation of 150mg once daily dose
- The patient is not pregnant
- The patient does not have moderate hepatic impairment (Child-Pugh class B)
- The patient is not concomitantly taking an OATP 1B1 inhibitor (i.e. gemfibrozil, cyclosporine, ritonavir, rifampin)
- The patient has experienced a clinically significant improvement in endometriosis-associated pain
- Treatment duration has not exceeded a total of 24 months

Approval will be for up to **18 months.**

II. Myfembree (relugolix/estradiol/norethindrone) may be considered **medically necessary** for the continuation of treatment of moderate to severe pain associated with endometriosis when the following criteria are met:

- The patient meets all the initial criteria for approval
- The patient has experienced a clinically significant improvement in endometriosis-associated pain
- Treatment duration has not exceeded a total of 24 months

Approval will be for up to **18 months.**

III. Myfembree (relugolix/estradiol/norethindrone) and Oriahnn (elagolix/estradiol/norethindrone and elagolix) may be considered **medically necessary** for the continuation of treatment of heavy menstrual bleeding associated with uterine leiomyomas (i.e., fibroids) in premenopausal women when the following criteria are met:

- The patient meets all the initial criteria for approval
- The patient has experienced a noticeable clinical benefit since initiating therapy with the requested medication (i.e., positive response as measured by pictorial blood loss assessment chart, menstrual pictogram, pad count, self-perception, etc.).
- Treatment duration has not exceeded a total of 24 months

Approval will be for up to **18 months.**

Dosing and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits

Orilissa 200 mg tablets – 56 tablets per 28 days
Orilissa 150 mg tablets – 28 tablets per 28 days
Oriahnn – 56 capsules per 28 days
Myfembree – 28 tablets per 28 days

Coverage Duration
Orilissa

- 24 months for patients with no coexisting conditions using 150 mg once daily dosing
- 6 months for patients with moderate hepatic impairment (Child-Pugh Class B) using 150 mg once daily dosing
- 6 months for patients with dyspareunia using 200mg twice daily dosing

Oriahnn and Myfembree

- 24 months per member lifetime

CLINICAL RATIONALE

The intent of the criteria is to provide coverage consistent with product labeling, FDA guidance, standards of medical practice, evidence-based drug information, and/or published guidelines. Myfembree 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 in premenopausal women.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often the first-line treatment for endometriosis, followed by hormone therapy. If NSAIDs and hormonal contraceptives are ineffective, then the next step is treatment with a gonadotropin-releasing hormone (GnRH) analogue such as leuprolide, goserelin (Zoladex), or nafarelin (Synarel). GnRH analogues may have significant side effects, including hot flushes, vaginal dryness, and osteopenia. Osteopenia has been shown to be reversible with short-term use but may not be with long-term use or use of multiple cycles. Due to risk of osteopenia and bone loss, Myfembree will not be approved if the patient has received a 12-month treatment course of Lupron Depot or Lupaneta Pack or a 6-month treatment course of Zoladex or Synarel.

Danazol, an androgen, is effective in the treatment of pelvic pain associated with endometriosis. However, androgenic adverse effects, such as acne, hirsutism, and male pattern baldness often limit its use. The drug has several United States Food and Drug Administration boxed warnings, including the risk of thrombosis and teratogenicity. Due to significant adverse effects, a trial of Danazol is not required.

Use of elagolix-containing drugs (e.g., Oriahnn [elagolix/estradiol/norethindrone], Orilissa [elagolix]) and relugolix-containing drugs (e.g., Myfembree [relugolix/estradiol/norethindrone]) should be limited due to the risk of continued bone loss, which may not be reversible. Oriahnn, Orilissa and Myfembree are contraindicated in women with known osteoporosis and may cause a decrease in bone mineral density (BMD) in some patients. BMD loss is greater with increasing duration of use and may not be completely reversible after stopping treatment. For Orilissa, the decrease in BMD is dose-dependent. The maximum recommended treatment duration is 24 months for patients taking Myfembree, Oriahnn, or Orilissa 150mg once daily. The maximum recommended treatment duration is 6 months for patients taking Orilissa 200mg twice daily. Therefore, Myfembree will not be approved if the patient has already received greater than or equal to 24 cumulative months of treatment with elagolix-containing and/or relugolix-containing products OR greater than or equal to 6 months of treatment with Orilissa 200mg twice daily. The duration of approval will be entered based upon the patient's previous use with elagolix-containing and/or relugolix-containing products; the total cumulative amount of time that the patient will be approved for elagolix-containing and/or relugolix-containing products will not exceed 24 months.

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

- Code(s), if applicable

REFERENCES

- Oriahnn [package insert]. North Chicago, IL: Abbvie, Inc.; May 2020.
- Myfembree [package insert]. Brisbane, CA: Myovant Sciences, Inc.; August 2022.
- Orilissa [package insert]. North Chicago, IL: AbbVie Inc.; February 2021
- New Drug Review: Oriahnn (elagolix/estradiol/norethindrone and elagolix) Oral Capsules. IPD Analytics. Accessed September 2020.
- New Drug Review: Myfembree (relugolix/estradiol/norethindrone) Oral Tablets. IPD Analytics. Accessed June 18, 2021.
- Oriahnn (elagolix/estradiol/norethindrone and elagolix) oral capsules Condensed Drug Monograph. CVS Caremark Pharmacy & Therapeutics. Accessed September 2020.
- De La Cruz MSD & Buchanan EM. Uterine Fibroids: Diagnosis and Treatment. *Am Fam Physician*. 2017;95(2):100-107. Available at: https://www.aafp.org/afp/2017/0115/p100.html. Accessed September 8, 2020.
- Agency for Healthcare Research and Quality (AHRQ). Management of uterine fibroids. Comparative effectiveness review no. 195. 2017 December. URL: https://effectivehealthcare.ahrq.gov/topics/uterine-fibroids/research-2017. Available from Internet. Accessed 2020 July 7.
- American College of Obstetricians and Gynecologists (ACOG). Uterine fibroids. Frequently asked questions: gynecologic problems. December 2018. URL: https://www.acog.org/patient-resources/faqs/gynecologic-problems/uterine-fibroids. Available from Internet. Accessed 2020 July 2.
- Borah BJ, Nicholson WK, Bradley L et al. The impact of uterine leiomyomas: a national survey of affected women. *Am J Obstet Gynecol.* 2013;209(4):319.e1-319.e20.
- De La Cruz M and Buchanan E. Uterine fibroids: diagnosis and treatment. *Am Fam Physician.* 2017; 95(2):100-7.
- Food and Drug Administration (FDA). Drugs@FDA. URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Available from Internet. Accessed 2020 July 1.
- Lupron Depot 3.75 mg prescribing information. North Chicago, IL: AbbVie Inc.; 2013 October.
- Lupron Depot 11.25 mg prescribing information. North Chicago, IL: AbbVie Inc.; July 2022.
- National Women's Health Network (NWHN). The long road to long-term treatment: evaluating the state of uterine fibroids medication. URL: https://www.nwhn.org/the-long-road-to-long-term-treatment-evaluating-the-state-of-uterine-fibroids-medication/. Available from Internet. Accessed 2020 June 30.
- Office on Women's Health (OWH). Uterine fibroids. 2019 April. URL: https://www.womenshealth.gov/a-z-topics/uterine-fibroids. Available from Internet. Accessed 2020 June 30.
- Orilissa prescribing information. North Chicago, IL: AbbVie Inc.; 2019 August.
- RxPipeline. Available with subscription at https://www.caremark.com/wps/portal/client. Accessed 2020 July 1.
- Schlaff W, Ackerman R, Al-Hendy A et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. *N Engl J Med.* 2020; 382(4):328-40.
- Simon J, Al-Hendy A, Archer D et al. Elagolix treatment for up to 12 months in women with heavy menstrual bleeding and uterine leiomyomas. *Obstet Gynecol.* 2020; 135(6):1313-26.

- Stewart EA, et al. Relugolix combination therapy reduced uterine fibroid-associated pain in two Phase 3 LIBERTY studies. Obstet Gynecol. 2020;135(5 suppl):27S.
- Al-Hendy A, et al. Treatment of uterine fibroid symptoms with relugolix combination therapy. N Engl J Med. 2021;384(7):630-642.
- Al-Hendy A et al. LIBERTY: Long-term extension study demonstrating one-year efficacy and safety of relugolix combination therapy in women with symptomatic uterine fibroids. Fertil Steril. 2020;114(3 suppl):E1. doi:10.1016/j.fertnstert.2020.08.027
- Orilissa [package insert]. North Chicago, IL: AbbVie Inc.; August 2019.
- Schrager S, Falleroni J, Edgoose J. Evaluation and treatment of endometriosis. Am Fam Physician. 2013 Jan 15;87(2):107-13.
- Management of endometriosis. Practice Bulletin No. 114. American College of Obstetricians and Gynecologists. Obstet Gynecol 2010;116:223-36.
- Samy A, Taher A, Sileem SA et al. Medical therapy options for endometriosis related pain, which is better? A systematic review and network meta-analysis of randomized controlled trials. *J Gynecol Obstet Hum Reprod*. 2020;101798. doi: 10.1016/j.jogoh.2020.101798. Online ahead of print.

Some content reprinted from CVS Health

POLICY HISTORY

Policy #: 05.04.17
Original Effective Date: December 18, 2020
Reviewed: October 2022
Revised: October 2022
Current Effective Date: November 27, 2022