Drug Monograph

Drug Name: **Myfembree® (relugolix, estradiol, and norethindrone acetate) tablet**

Drug Class: **Endocrine and Metabolic Agents: Luteinizing Hormone Releasing Hormone (LHRH), Gonadotropin Releasing Hormone (GnRH) Antagonists, Oral**

Prepared For: MO HealthNet

Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Myfembree is available as an oral tablet containing 40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate.
Manufacturer:	Distributed by: Myovant Sciences, Brisbane, CA 94005.
Summary of Findings:	The efficacy and safety of Myfembree for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women was demonstrated in two replicate, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 patients. The primary endpoint was the proportion of women who achieved menstrual blood loss volume of <80 mL and at least a 50% reduction from the baseline volume of menstrual blood loss at 24 weeks. Both studies showed a statistically significant difference in the Myfembree-treated group when compared to placebo [55.3% and 56.5% respectively; 95% CI: 44.2%, 65.6% and 46.6%, 66.5% respectively (p<0.0001)].
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Uterine fibroids are benign tumors that originate from uterine smooth muscle tissue and are extremely common. Uterine fibroids can affect up to 70% to 80% of women by 50 years of age. Roughly 25% of women with uterine fibroids experience symptoms including heavy menstrual bleeding, anemia, pelvic pressure, pain, urinary and gastrointestinal symptoms, adverse pregnancy outcomes, and infertility. The primary management for uterine fibroids is hysterectomy, however fertility-sparing medication options that provide symptomatic relief are generally first-line management.

Dosage Form [3]

Myfembree is available as an oral tablet containing 40 mg of relugolix, 1 mg of estradiol, and 0.5 mg of norethindrone acetate.

Manufacturer [3]

Distributed by: Myovant Sciences, Brisbane, CA 94005.

Indication(s) [3]

Myfembree is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

Clinical Efficacy [3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Myfembree is a combination of relugolix, estradiol, and norethindrone acetate. Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased serum concentrations of the ovarian sex hormones estradiol and progesterone and reducing bleeding associated with uterine fibroids. Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a component of Myfembree, the addition of exogenous estradiol may reduce the increase in bone resorption and resultant bone loss that can occur due to a decrease in circulating estrogen concentrations from relugolix alone. Progestins such as norethindrone act by binding to nuclear receptors that are expressed in progesterone-responsive tissues. As a component of Myfembree, norethindrone may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

Pharmacokinetics:

	Relugolix	Unconjugated Estradiol	Norethindrone
Absorption	12%	Well absorbed	64%

Metabolism	Metabolized by CYP3A (primary) and CYP2C8 (lesser extent)	Converted to estrone reversibly, and both can be converted to estriol, which is a major urinary metabolite. Also, undergoes enterohepatic recirculation due to sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine and hydrolysis in the intestine.	Extensive biotransformation, primarily reduction, in addition to sulfation, glucuronidation, and oxidation, respectively, by sulfotransferases, glucuronosyltransferases and CYP enzymes.
Excretion	Feces: 81% Urine: 4.1%	Urine	Urine
Half-life	25 hours	NA	8-9 hours

Clinical Trials Experience

STUDY 1 DESIGN (LIBERTY 1, NCT 03049735))	Randomized, multinational, double-blind, placebo-controlled (N=388)
INCLUSION CRITERIA	• Premenopausal female aged 18 to 50 years old • Has regularly occurring menstrual periods of ≤ 14 days duration with a cycle of 21 to 38 days from the start of one menstrual period until the start of the next, by participant history for at least 3 months prior to the first screening visit. • Has a diagnosis of uterine fibroids that is confirmed by a transvaginal and/or transabdominal ultrasound performed during the screening period. • Has heavy menstrual bleeding associated with uterine fibroids as evidenced by a menstrual blood loss (MBL) of ≥ 160 mL during one cycle or ≥ 80 mL per cycle for two menstrual cycles as measured by the alkaline hematin method during the screening period.
EXCLUSION CRITERIA	• Has transvaginal and/or transabdominal ultrasound during the screening period demonstrating pathology other than uterine fibroids that could be responsible for or contributing to the patient's heavy menstrual bleeding. • Has known rapidly enlarging uterine fibroids in the opinion of the investigator. • Has a weight that exceeds the weight limit of the DXA scanner or has a condition that precludes an adequate DXA measurement at the lumbar spine and proximal femur. • Has a history of or currently has osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa, or low traumatic (from the standing position) or atraumatic fracture (toe, finger, skull, face and ankle fractures are allowed). • Has a history of the use of bisphosphonates, calcitonin, calcitriol, ipriflavone, teriparatide, denosumab, or any medication other than

	calcium and vitamin D preparations to treat bone mineral density loss.
TREATMENT REGIMEN	Patients were randomized 1:1:1 to receive Myfembree (n=122) once daily for 24 weeks, placebo (n=113) once daily for 24 weeks, or Relugolix 40 mg monotherapy (n=125) for 12 weeks, then Myfembree for 12 weeks.
RESULTS	The primary endpoint was the proportion of women who achieved MBL volume of <80 mL and at least a 50% reduction from the baseline volume of MBL at 24 weeks. In this study, 72.1% of Myfembree-treated patients achieved the primary endpoint vs 16.8% of placebo-treated patients with a difference from placebo of 55.3% (95% CI: 44.2%, 65.6%; p<0.0001).
SAFETY	Discussed in the Adverse Effects section below.

STUDY 2 DESIGN (LIBERTY 2, NCT03103087)	Randomized, multinational, double-blind, placebo-controlled (N=382)
INCLUSION CRITERIA	• Same as above
EXCLUSION CRITERIA	• Same as above
TREATMENT REGIMEN	Patients were randomized 1:1:1 to receive Myfembree (n=122) once daily for 24 weeks, placebo (n=113) once daily for 24 weeks, or Relugolix 40 mg monotherapy (n=125) for 12 weeks, then Myfembree for 12 weeks.
RESULTS	The primary endpoint was the proportion of women who achieved MBL volume of <80 mL and at least a 50% reduction from the baseline volume of MBL at 24 weeks. In this study, 71.2% of Myfembree-treated patients achieved the primary endpoint vs 14.7% of placebo-treated patients with a difference from placebo of 56.5% (95% CI: 46.6%, 66.5%; p<0.0001).
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [3,4]

- **Black Boxed Warning: Contraindicated in women with current or a history of thrombotic or thromboembolic disorders and in women at increased risk for these events, including women over 35 years of age who smoke or women with uncontrolled hypertension.**
- Pregnancy
- Known osteoporosis
- Current or history of breast cancer or other hormone-sensitive malignancies
- Known hepatic impairment or disease
- Undiagnosed abnormal uterine bleeding
- Known hypersensitivity to components of Myfembree

Warnings and Precautions [3,4]

- **Black Boxed Warning: Estrogen and progestin combination products increase the**

risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in women at increased risk for these events.

- Discontinue if there is a sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately.
- Bone Loss: Decreases in bone mineral density (BMD) that may not be completely reversible. Baseline and periodic BMD assessments are recommended. Assess risk-benefit for women with additional risk factors for bone loss.
- Depression, Mood Disorders, and Suicidal Ideation: Advise patients to seek medical attention for new onset or worsening depression, anxiety, or other mood changes
- Hepatic Impairment and Transaminase Elevations: Counsel patients on signs and symptoms of liver injury.
- Elevated Blood Pressure: Do not use in women with uncontrolled hypertension. For women with well-controlled hypertension, continue to monitor blood pressure and stop Myfembree if blood pressure rises significantly.
- Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy: Advise women to use non-hormonal contraception during treatment and for one week after discontinuing Myfembree. Myfembree may delay the ability to recognize pregnancy because it alters menstrual bleeding. Perform testing if pregnancy is suspected and discontinue Myfembree if pregnancy is confirmed.
- Risk of Early Pregnancy Loss: Can cause early pregnancy loss.
- Uterine Fibroid Prolapse or Expulsion: Advise patients to see medical attention for severe uterine bleeding.
- Hypersensitivity reactions: Discontinue immediately if hypersensitivity reaction occurs.

Adverse Effects [3,4]

Most common, ≥ 3%	Myfembree (N=254) %	Placebo (N=256) %
Hot flush, hyperhidrosis, or night sweats	10.6	6.6
Abnormal uterine bleeding	6.3	1.2
Alopecia	3.5	0.8
Libido decreased	3.1	0.4

Drug Interactions [3,4]

- Effect of other drugs on Myfembree:
  - Coadministration of Myfembree with P-gp inhibitors increases the area under the curve (AUC) and maximum concentration of relugolix and may increase the risk of adverse reactions associated with Myfembree. Avoid use of Myfembree with oral P-gp inhibitors. If use is unavoidable, take Myfembree first, separate dosing by at least 6 hours, and monitor patients for adverse reactions.
  - Use of Myfembree with combined P-gp and strong CYP3A inducers decreases the AUC and maximum concentration of relugolix, estradiol, and norethindrone. Avoid use of Myfembree with combined P-gp and strong CYP3A inducers.

Dosage and Administration [3,4]

- Take 1 tablet by mouth once daily

- Take missed dose as soon as possible the same day and then resume regular dosing the next day the usual time
- If concomitant use of oral P-gp inhibitors is unavoidable, take Myfembree at least 6 hours before taking the P-gp inhibitor.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Relugolix, estradiol, and norethindrone acetate	Myfembree®	Myovant Sciences	1 tablet daily (relugolix 40 mg, estradiol 1 mg, norethindrone 0.5 mg)	$1,058
Elagolix, estradiol, and norethindrone acetate	Oriahnn®	AbbVie Inc	1 tablet twice daily (elagolix 300 mg, estradiol 1 mg, norethindrone 0.5mg in the morning; elagolix 300 mg in the evening)	$1,058

** Wholesale Acquisition Cost

Conclusion

Myfembree, an oral gonadotropin-releasing hormone antagonist, is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. The safety and efficacy of Myfembree was demonstrated in two randomized, double-blind, placebo-controlled trials that enrolled 768 patients with uterine fibroids. Myfembree showed a statistically significant difference, when compared to placebo, on proportion of women who achieved menstrual blood loss volume of <80 ml and at least a 50% reduction from baseline volume of menstrual blood loss. The most common adverse reactions (≥3%) with Myfembree were hot flushes, hyperhidrosis, uterine bleeding, alopecia, and decreased libido.

Recommendation

The MO Healthnet Division recommends adding this drug to the current Elagolix clinical edit.

References

1) Uterine fibroids. U.S. Department of Health & Human Services. womenshealth.gov. Accessed July 2, 2021.
2) IPD Analytics. New Drug Review: Myfembree. ipdanalytics.com. Accessed July 2, 2021. f
3) Product Information: Myfembree® (relugolix, estradiol, and norethindrone acetate) 2021. Myovant Sciences, Brisbane, CA 94005.
4) LIBERTY 1: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids. NCT03049735. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03049735. Accessed July 2, 2021.
5) LIBERTY 2: An International Phase 3 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study to Evaluate Relugolix Co-Administered With and Without Low-Dose Estradiol and Norethindrone Acetate in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroids. NCT03103087. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03103087. Accessed July 2, 2021.

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