PDL DRUG REVIEW

Proprietary Name: Myfembree®
Common Name: relugolix, estradiol, & norethindrone acetate
PDL Category: Estrogen Combos

Comparable Products	Preferred Drug List Status
Oriahnn	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Myfembree® is a fixed-dose combination of relugolix (a non-peptide small molecule gonadotropin-releasing hormone [GnRH] receptor antagonist), estradiol (E2, an estrogen), and norethindrone acetate (NETA, a progestin).

Relugolix is a GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thus reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased serum concentrations or the ovarian sex hormones estradiol and progesterone and reduced bleeding associated with uterine fibroids. Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. 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 act by binding to nuclear receptors that are expressed in progesterone-responsive tissues. Norethindrone may protect the uterus from the potential adverse endometrial effects of unopposed estrogen.

Indication: For the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Use of Myfembree® should be limited to 24 months due to the risk of continued bone loss which may not be reversible.

There is no pregnancy category for this medication; however, the risk summary indicates that use is contraindicated in pregnancy. Based on findings from animal studies and its mechanism of action, Myfembree® may cause early pregnancy loss. Discontinue use if pregnancy occurs during treatment. The limited human data with use in pregnant women are not sufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Myfembree® during pregnancy. Pregnant females exposed to Myfembree® and healthcare providers are encouraged to call the Myfembree® Pregnancy Exposure Registry at 1-855-428-0707. Exclude pregnancy before starting treatment with Myfembree®. Advise women of reproductive potential to use effective non-hormonal contraception during treatment and for 1 week following discontinuation. Avoid concomitant use of hormonal contraceptives with Myfembree®. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets, containing a fixed-dose combination of 40mg relugolix, 1mg estradiol (E2), and 0.5mg norethindrone acetate (NETA)

Recommended Dosage: Prior to initiation of Myfembree®, exclude pregnancy and discontinue hormonal contraceptives.

Take one tablet PO QD at about the same time every day, with or without food. Start Myfembree® as early as possible after the onset of menses but no later than 7 days after menses has started. The recommended total duration of treatment with Myfembree® is 24 months. Use is contraindicated in women with hepatic impairment or disease.

Drug Interactions: Co-administration of Myfembree® with P-gp inhibitors increases the AUC and max concentration (Cmax) 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 Cmax of relugolix, estradiol, and/or norethindrone and may decrease the therapeutic effects of Myfembree®. Avoid use of Myfembree® with combined P-gp and strong CYP3A inducers.

Box Warning: Myfembree® has a box warning regarding thromboembolic disorders and vascular events. Estrogen and progestin combination products, including Myfembree®, increase the risk of thrombotic or thromboembolic disorders, including pulmonary embolism (PE), deep vein thrombosis (DVT), stroke, and myocardial infarction, especially in women at increased risk for these events. Myfembree® is 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.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Myfembree®) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than the placebo.* The most frequently reported adverse events included hot flush, hyperhidrosis, or night sweats (4%), abnormal uterine bleeding (5.1%), alopecia (2.7%), and libido decreased (2.7%). Adverse reactions reported in at least 2% and less than 3% of women in the Myfembree® group and greater incidence than placebo included irritability, dyspepsia, and breast cyst. Other important adverse reactions reported in women treated with Myfembree® included one serious reaction each of uterine myoma expulsion (0.4%), and uterine leiomyoma (prolapse; 0.4%).

The mean percent change from baseline in lumbar spine bone mineral density (BMD) in women with uterine fibroids at month 6 in Studies L1 and L2 (phase 3 studies) was 0.18% with placebo vs -0.23% with Myfembree®. Use is contraindicated in women with known osteoporosis. Consider the benefits and risks of Myfembree® treatment in patients with a history of a low trauma fracture or risk factors for osteoporosis or bone loss, including taking medications that may decrease BMD. Assessment of BMD is recommended at baseline and periodically thereafter. Consider discontinuing treatment if the risk associated with bone loss exceeds the potential benefit of treatment. While the effect of supplementation with calcium and vitamin D was not studied, such supplementation for patients with inadequate dietary intake may be beneficial. The impact of BMD decreases on long-term bone health and future fracture risk in premenopausal women is not known.

Myfembree® was associated with adverse mood changes. A greater proportion of women treated with Myfembree® compared to placebo reported depression (2.4% vs 0.8%), irritability (2.4% vs 0%), and anxiety (1.2% vs 0.8%). Promptly assess patients with mood changes and depressive symptoms including shortly after starting treatment, to determine whether the risks of continued treatment with Myfembree® outweigh the benefits. Advise patients to seek immediate medical attention for suicidal ideation and behavior.

Instruct women to seek medical attention for signs and symptoms that may reflect liver injury. Acute liver test abnormalities may necessitate the discontinuation of Myfembree® use until the liver tests return to normal and Myfembree® causation has been excluded. Use is contraindicated in known hepatic impairment or disease.

Discontinue Myfembree® if signs or symptoms of gallbladder disease or jaundice occur. Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease.

For women with well-controlled hypertension, continue to monitor blood pressure and stop Myfembree® if blood pressure rises significantly. Use is contraindicated in women with uncontrolled hypertension.

Consider discontinuing Myfembree® if hair loss becomes a concern. In phase 3 trials, more women experienced alopecia, hair loss, and hair thinning (3.5%) with Myfembree® compared to placebo (0.8%).

More frequent monitoring in Myfembree®-treated women with prediabetes and diabetes may be necessary. Myfembree® may decrease glucose tolerance and result in increased blood glucose concentrations. Monitor lipid levels and consider discontinuing treatment if hypercholesterolemia or hypertriglyceridemia worsens. Use of Myfembree® is associated with increases in total cholesterol and LDL-C. In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations in triglyceride levels leading to pancreatitis.

Patients with hypothyroidism and hypoadrenalism may require higher doses of thyroid hormone or cortisol replacement therapy. The use of estrogen and progestin combinations may raise serum concentrations of binding proteins, which may reduce free thyroid or corticosteroid hormone levels. The use of estrogen and progestin may also affect the levels of sex hormone-binding globulin, and coagulation factors.

Contraindications: In women:

- With a 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
    - Current or history of deep vein thrombosis or pulmonary embolism
    - Vascular disease
    - Thrombogenic valvular or thrombogenic rhythm diseases of the heart
    - Inherited or acquired hypercoagulopathies
    - Uncontrolled hypertension
    - Headaches with focal neurological symptoms or migraine headaches with aura if >35 years of age
- Who are pregnant
- With known osteoporosis, because of the risk of further bone loss
- With current or history of breast cancer or other hormone-sensitive malignancies, and with increased risk for hormone-sensitive malignancies
- With known hepatic impairment or disease
- With undiagnosed abnormal uterine bleeding
- With known anaphylactic reaction, angioedema, or hypersensitivity to Myfembree® or any of its components

Manufacturer: Myovant Sciences (Myovant and Pfizer will jointly commercialize Myfembree®)

Analysis: The safety and efficacy of Myfembree® were assessed in two replicate, 24-week, multinational, randomized, double-blind, placebo-controlled trials (Study LI and Study L2) that included premenopausal women (N=768) with heavy menstrual bleeding associated with uterine fibroids. For study inclusion, women had to have uterine fibroids confirmed by ultrasound exam in which at least one fibroid met at least one of the following:

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

Women also had to have menstrual blood loss (MBL) volume of ≥80ml per cycle for 2 menstrual cycles or ≥160ml during one cycle quantified by the alkaline hematin method from menstrual products collected during baseline menstrual cycles to be included in the studies. Iron therapy was required for women with hemoglobin ≥8g/dL and ≤10g/dL. Women were allowed, but not required, to take calcium and vitamin D during the study.

In both studies, women were randomized to receive a relugolix 40mg tablet QD plus an over encapsulated tablet of E2 1mg and NETA 0.5mg (relugolix + E2/NETA), which is equivalent to 1 tablet of Myfembree®, for 24 weeks, placebo for 24 weeks, or relugolix 40mg monotherapy for 12 weeks followed by Myfembree® for 12 weeks. Treatment was initiated within the first 7 days after the onset of menses. The median age of included women was 43 years, while 53% were Black, and the mean BMI was 31.6kg/m^2. Across studies at baseline, mean MBL volume at baseline was 231ml. Baseline uterine size in Studies L1 and L2 ranged from normal to greater than 28 weeks gestation size.

The primary endpoint was the proportion of women in the Myfembree® group compared with women in the placebo group, who achieved menstrual blood loss (MBL) volume of <80ml and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment, as measured by alkaline hematin method. Key secondary endpoints were related to amenorrhea, MBL volume, and change in hemoglobin.

In both Study L1 and Study L2, results suggested a statistically higher proportion of women treated with Myfembree® achieved the primary endpoint of both an MBL volume of less than 80ml and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with placebo. Results can be seen in the table below, which was adapted from the prescribing information.

	Study L1		Study L2	
	Myfembree® (N=122)	Placebo (N=113)	Myfembree® (N=125)	Placebo (N=129)
Women w/MBL volume <80ml & ≥50% reduction in MBL volume from baseline to last 35 days of treatment	72.1%	16.8%	71.2%	14.7%
Difference from placebo (%), p-value	55.3%; p<0.0001		56.5%; p<0.0001	
NNT *calculated by Change Healthcare*	2		2	

In Studies L1 and L2, 50.0% and 50.4% of women treated with Myfembree®, respectively, achieved amenorrhea compared to 6.2% and 3.1% treated with placebo, respectively, over the last 35 days of treatment.

The mean MBL volumes in Studies L1 and L2 at baseline were 243.8ml and 246.7ml in the Myfembree® group and 223.2ml and 211.8ml in the placebo group, respectively. The mean reduction in MBL volume from baseline to week 24 in the Myfembree® group was 82% in Study L1 and 84.3% in Study L2 compared with placebo which was 19.1% and 15.1%, respectively.

For efficacy, a hemoglobin response was defined as a hemoglobin increase >2g/dL from baseline to week 24 in the subgroup of women with anemia at baseline (hemoglobin ≤10.5g/dL). A statistically higher proportion treated with Myfembree® compared with placebo had >2g/dL improvement in hemoglobin levels. Results can be seen in the table below, which was adapted from the prescribing information.

Proportion of women with baseline Hgb ≤10.5 and >2g/dL improvement in hemoglobin levels from baseline at week 24	Study L1		Study L2	
	Myfembree® n=43 (N=122)	Placebo n=29 (N=113)	Myfembree® n=40 (N=125)	Placebo n=53 (N=129)
% at week 24	44.2%	17.2%	55.0%	5.7%
Difference from placebo (%), p-value	26.9%; p=0.0177		49.3%; p<0.0001	
NNT *calculated by Change Healthcare*	4		3	

n=number of patients with Hgb ≤10.5g/dL at baseline N=number of patients in each treatment group

Place in Therapy: Myfembree® is a fixed-dose combination tablet containing relugolix, estradiol, and norethindrone acetate indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Use of Myfembree® should be limited to 24 months due to the risk of continued bone loss which may not be reversible. It has a box warning regarding increased risk of thromboembolic disorders and vascular events. In two double-blind, placebo-controlled studies that included premenopausal women with heavy menstrual bleeding associated with uterine fibroids, relugolix 40mg +E2 1mg/NETA 0.5mg (which is the equivalent to 1 tablet of Myfembree®) was compared with placebo for 24 weeks. A statistically higher proportion of women treated with Myfembree® achieved the primary endpoint of both MBL volume of less than 80ml and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with placebo.

Oriahnn® (with the active ingredients of elagolix (a GnRH receptor antagonist), E2, and NETA) has the same indication as Myfembree®, but Oriahnn® is to be taken twice daily while Myfembree® can be taken once daily.[2]

There is no evidence at this time to support that Myfembree® is safer or more effective than the other medications. It is recommended that Myfembree® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Preferred**
- ☒ **Non-Preferred with Conditions**

References

[1] Myfembree [package insert]. Brisbane, CA: Myovant Sciences; 2021.
[2] Oriahnn [package insert]. North Chicago, IL: AbbVie Inc; 2020.