NEW DRUG APPROVAL

Brand Name	Myfembree®
Generic Name	relugolix, estradiol, and norethindrone acetate
Drug Manufacturer	Myovant Sciences, Inc.

New Drug Approval

FDA Approval Date: May 26, 2021

Review designation: Standard

Type of review: Type 4 - New Combination, New Drug Application (NDA): 214846

Dispensing restrictions: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Uterine leiomyomas are the most common pelvic tumor in females. Incidence is difficult to determine since there are few longitudinal studies. In addition, the actual prevalence is unknown since studies have been conducted mainly in symptomatic patients or following hysterectomy. Representative studies include:

- In the Nurses' Health Study II, a large prospective study in the United States, over 95,000 women ages 25 to 44 were followed from 1989 to 1993. The age-standardized incidence rates of fibroids confirmed by ultrasound or hysterectomy were 9.2 per 1000 woman-years overall, 30.6 for Black women, and 8.9 for White women. Overall incidences by age group were: 25 to 29 (3.3 per 1000 woman-years), 30 to 34 (6.8), 35 to 39 (10.3), and 40 to 44 (16.0).
- In a population-based study of an urban health plan in Washington, DC, 1364 women ages 35 to 49 years were randomly selected and assessed by survey and/or ultrasound. Newly detected fibroids were present in 59 percent of Black women and 43 percent of White women; for women in their late 40s, the estimated frequency of fibroids was >80 percent and near 70 percent for Black and White women, respectively.
- A cross-sectional study in Europe of 1756 women with fibroid-related symptoms found myomas in 12 to 24 percent. Myomas are clinically apparent in approximately 12 to 25 percent of reproductive-age women and noted on pathologic examination in approximately 80 percent of surgically excised uteri.
- A study of 100 hysterectomy specimens found myomas in 77 percent of uterine specimens. Most women had multiple myomas, with an average of 7.6 fibroids.
- An ultrasound screening study of women aged 18 to 30 found a prevalence of 26 percent in Black women and 7 percent in White women.

The prevalence of leiomyomas increases with age during the reproductive years. Leiomyomas have not been described in prepubertal girls, but they are occasionally noted in adolescents. Most, but not all, patients have shrinkage of leiomyomas after menopause.

Efficacy

In both Study L1 and Study L2, a statistically higher proportion of women treated with Myfembree® achieved the primary endpoint of both an MBL volume of less than 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with placebo.

Table 5: Proportion of Responders for Reduction in MBL Volume Over Last 35 days of Treatment in Women with Uterine Fibroids (Studies L1 and L2)

	Study L1		Study L2	
	MYFEMBREE (N = 122)	Placebo (N = 113)	MYFEMBREE (N = 125)	Placebo (N = 129)
Women with MBL Volume < 80 mL and ≥50% Reduction in MBL Volume from Baseline to the Last 35 Days of Treatment	72.1%	16.8%	71.2%	14.7%
Difference from placebo, % 95% CI* p-value	55.3% (44.2%, 65.6%) < 0.0001		56.5% (46.6%, 66.5%) < 0.0001	

*CI = confidence interval.

Safety

ADVERSE EVENTS

Most common adverse reactions (incidence ≥ 3%) are hot flush, hyperhidrosis or night sweats, uterine bleeding, alopecia, and decreased libido.

WARNINGS & PRECAUTIONS

- Bone loss
- Suicidal ideation and mood disorders
- Hepatic impairment and transaminase elevations
- Elevated blood pressure
- Change in menstrual bleeding pattern and reduced ability to recognize pregnancy
- Risk of early pregnancy loss
- Uterine fibroid prolapse or expulsion
- Hypersensitivity reactions

CONTRAINDICATIONS

- High risk of arterial, venous thrombotic, or thromboembolic disorder.
- Pregnancy.
- Known osteoporosis.
- Current or history of breast cancer or other hormone-sensitive malignancies.
- Known hepatic impairment or disease.
- Undiagnosed abnormal uterine bleeding.

Clinical Pharmacology

MECHANISMS OF ACTION

Myfembree® is a combination of relugolix, estradiol (E2), and norethindrone acetate (NETA). 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 reduced 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.

Dose & Administration

ADULTS

- Exclude pregnancy and discontinue hormonal contraceptives prior to Myfembree® initiation.
- Take one tablet orally once daily.
- Take the missed dose of Myfembree® as soon as possible the same day and then resume regular dosing the next day at 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.

PEDIATRICS

Safety and effectiveness of Myfembree® in pediatric patients have not been established.

GERIATRICS

Not approved for use in postmenopausal patients.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: fixed-dose combination containing relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg.