

Company

Myovant Sciences

Drug or Device Name

Myfembree®

Category

Pharmaceutical

Compound/Technical Name

not applicable

Trade Name

Myfembree®

Date of Approval

05/26/2021

Therapeutic Categories

N/A

Indications

On May 26, 2021, the FDA approved the first oral, once-daily gonadotropin-releasing hormone (GnRH) receptor antagonist combination, Myfembree® (relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg), for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids (UF) in premenopausal women, with a treatment duration of up to 24 months. UF, also known as leiomyomas or myomas, are benign tumors of the uterus whose growth is dependent on estrogen and progesterone. The prevalence of fibroids has been historically underestimated by epidemiologic studies, which have focused mainly on symptomatic women, leaving behind a considerable population of asymptomatic women as well as those with underreported symptoms. With a cumulative incidence of >70% by the age of 50, UF are common and often appear in women during childbearing years. There are notable prevalence differences among races, with fibroids more common, greater in number, and larger in women of African ancestry versus white or Asian women. Symptoms are present in ~25% of women, with the most common being HMB, often associated with anemia. The most debilitating issue for women with UF is the associated pain. Relatively little is known about the specific molecular mechanisms that regulate fibroid development, growth, and regression. Current evidence suggests fibroids are biologically heterogeneous, with sex hormones, stem cells, glucocorticoids, growth factors, cytokine signaling, extracellular matrix remodeling, and epigenetic factors potentially involved in the pathogenesis of fibroids. Treatment should be individualized and specific to the tumor size and location, as well as the patient's age, symptoms, and desire to maintain fertility. Symptom relief, sustained reduction of the fibroid size, maintenance of fertility (if desired), and avoidance of harm should be four goals of treatment. Management can vary from pharmacological and minimally invasive treatments to surgery.

Background

Treatment of UF is a challenge with an immense economic burden in the US estimated to be in billions of dollars. Clinically, hormonal treatments have been explored for fibroid associated symptoms and potential to shrink the tumor. However, efficacy associated with hormonal treatments has been inadequate with a side effect profile that can prohibit long-term use. Meanwhile, surgery has been traditionally the standard treatment for UF. Younger women who have not started their families may not prefer the option of complete removal of uterus 'hysterectomy.' In addition, removal of tumor only 'myomectomy' may have a potential negative impact on the myometrium. GnRH agonists and antagonists have emerged as newer therapeutic options. After an initial stimulation of gonadotropin release ('flare effect'), GnRH agonists induce a pituitary downregulation which decreases the production of gonadotropins and gonadal steroids and inhibits further fibroid growth. GnRH agonists lead to amenorrhea in most women (>98%) and are associated with a 35%–65% decrease in fibroid size within 3 months of initiation. However, by medically inducing menopause, GnRH agonists are associated with adverse effects including hot flashes, mood swings, vaginal dryness, decreased libido, sleep disturbances, and bone loss in the case of long-term use (>6 months). To potentially alleviate some of these adverse effects, hormonal 'add-back' therapy can be used. Nonpeptide GnRH antagonists offer potential advantages, including oral administration, rapid effect without triggering initial receptor activation, and longer duration of use of up to 24 months when utilized as combination therapy to decrease side effects associated with low levels of estrogen and to help prevent any endometrial changes. GnRH receptor antagonists competitively bind to pituitary GnRH receptors and prevent binding of endogenous GnRH, which reduces the luteinizing hormone and follicle-stimulating hormone production. This action leads to decreased serum estradiol and progesterone concentrations thereby reducing UF induced HMB.

Development

Due to low aqueous solubility, identification of oral GnRH antagonists for development was challenging. However, in preclinical research relugolix was identified to have good GnRH binding specificity, and potent in vitro and in vivo GnRH antagonistic activity, without CYP inhibition. Relugolix competitively binds to pituitary GnRH receptors, blocking signaling of endogenous GnRH with reversible, dose dependent decreases in gonadotropin concentrations and subsequent ovarian estradiol and progesterone production suppression. GnRH antagonist monotherapy can result in hypoestrogenism and bone mineral density (BMD) loss so combination therapy is recommended. It is hypothesized that tissues vary in their sensitivity to estradiol and that maintenance of estradiol concentrations within the range of the early follicular phase (20-50 pg/mL) can decrease fibroid growth while minimizing hypoestrogenic effects. Therapeutic levels of systemic estradiol concentrations were maintained when relugolix 40 mg was co-administered with 1 mg estradiol and 0.5 mg norethindrone acetate, while the bone resorption and vasomotor symptoms associated with administration of relugolix alone were mitigated. Myovant's large Phase 3 clinical program for uterine fibroids consisted of two multinational, replicate, randomized, double-blind, placebo-controlled pivotal clinical studies (LIBERTY 1 and 2). In each study, ~390 women with HMB associated with UF were randomly assigned to receive once daily oral administration of Myfembree for 24 weeks, relugolix 40 mg for 12 weeks then Myfembree for 12 weeks, or placebo for 24 weeks. In the pivotal studies, Myfembree reduced menstrual blood loss volume and pain in women with UF and with a demonstrated safety profile. Women who completed one of the LIBERTY studies and met all eligibility criteria could enroll in an open-label long-term extension study—improvements in HMB, hemoglobin, and reduction of uterine and UF volume were sustained through up to 52 weeks of treatment with Myfembree and no new safety concerns were identified.

Innovation

Uterine fibroids (UF) are common benign, estrogen and progesterone dependent tumors of the uterus manifesting during a woman's reproductive years, with symptomatic cases often resulting in a surgical procedure, including ~250,000 hysterectomies and ~30,000 myomectomies in the US annually. Demand for less invasive approaches is growing, as is an increasing recognition of long-term risks of hysterectomy even with bilateral ovarian conservation. Recent guidelines suggest that patients should be counselled on all treatment options, both medical and surgical. Myfembree was developed to provide a novel, nonsurgical, uterine-sparing treatment option that is effective, with oral, once-daily dosing, and can be utilized longer-term. Myfembree represents the first FDA-approved once-daily pill that can reduce HMB associated with UF in premenopausal women with a treatment duration of up to 24 months. In the Phase 3 LIBERTY 1 and LIBERTY 2 studies, Myfembree demonstrated 72.1% and 71.2% response rates in menstrual blood loss at Week 24 compared with 16.8% and 14.7% women in the placebo groups, respectively (both $p < 0.0001$). A response was defined as a menstrual blood loss volume of less than 80 mL and a 50% or greater reduction from baseline in menstrual blood loss volume during the last 35 days of treatment measured using the alkaline hematin method. Women receiving Myfembree experienced reductions of 82.0% and 84.3% in menstrual blood loss from baselines, respectively (both $p < 0.0001$ compared to placebo, 19.1% and 15.1%). The New England Journal of Medicine recognized the importance of our Phase 3 LIBERTY program and published the study results. With this approval, women suffering with UF have a once-daily treatment option with demonstrated robust efficacy and safety.

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1. Al-Hendy A, Lukes AS, Poindexter III AN, et al. Treatment of Uterine Fibroid Symptoms with Relugolix Combination Therapy. *N Engl J Med*. 2021 Feb 18;384(7):630-642. doi: 10.1056/NEJMoa2008283. 2. Hunsche E, Rakov V, Scippa K, et al. The Burden of Uterine Fibroids from the Perspective of US Women Participating in Open-Ended Interviews. *Womens Health Rep (New Rochelle)*. 2022 Mar;3(1):286-296. doi: 10.1089/whr.2021.0086. 3. Osuga Y, Enya K, Kudou J, et al. Oral Gonadotropin-Releasing Hormone Antagonist Relugolix Compared with Leuporelin Injections for Uterine Leiomyomas: A Randomized Controlled Trial. *Obstet Gynecol*. 2019 Mar;133(3):423-433. doi: 10.1097/AOG.00000000000003141. 4. Osuga Y, Enya K, Kudou J, et al. Relugolix, a novel oral gonadotropin-releasing hormone antagonist, in the treatment of pain symptoms associated with uterine fibroids: a randomized, placebo-controlled, phase 3 study in Japanese women. *Fertil Steril*. 2019 Nov;112(5):922-929.e2. doi: 10.1016/j.fertnstert.2019.07.013. 5. Osuga Y, Seki Y, Tanimoto M, et al. Relugolix, an oral gonadotropin-releasing hormone receptor antagonist, reduces endometriosis-associated pain in a dose-response manner: a randomized, double-blind, placebo-controlled study. *Fertil Steril*. 2021 Feb;115(2):397-405. doi: 10.1016/j.fertnstert.2020.07.055. 6. Osuga Y, Seki Y, Tanimoto M, et al. Relugolix, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist, in women with endometriosis-associated pain: phase 2 safety and efficacy 24-week results. *BMC Womens Health*. 2021 Jun;21(1):250. doi: 10.1186/s12905-021-01393-3. 7. Stewart E, Lukes A, Venturella R, et al. Relugolix Combination Therapy for Uterine Leiomyoma-Associated Pain in the LIBERTY Randomized Trials. *Obstet. Gynecol*. 2022. Advance online publication. doi: <https://10.1097/AOG.00000000000004787>.

Attachments

- 1653677412Al-Hendy_et_al._-2020_-LIBERTY_Long-term_extension_study_demonstrating_o.pdf
- 1653677404Al-Hendy_et_al_NEJM_2021_LIBERTY_Manuscript.pdf
- 1653677270MYFEMBREE_PI.pdf

- 1653677262MYFEMBREE_FDA_Approval_Letter.pdf

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