HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MYFEMBREE safely and effectively. See full prescribing information for MYFEMBREE.

MYFEMBREE® (relugolix, estradiol, and norethindrone acetate) tablets, for oral use
Initial U.S. Approval: 2021

WARNING: THROMBOEMBOLIC DISORDERS AND VASCULAR EVENTS

See full prescribing information for complete boxed warning

- **Estrogen and progestin combinations, including MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders, especially in women at increased risk for these events. (5.1)**
- **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. (4)**

----------RECENT MAJOR CHANGES----------

Indications and Usage, Moderate to Severe Pain Associated with Endometriosis, (1.2)	08/2022
Warnings and Precautions, Hypersensitivity Reactions, (5.14)	01/2023

----------INDICATIONS AND USAGE----------

MYFEMBREE is a combination of relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol, an estrogen, and norethindrone acetate, a progestin, indicated in premenopausal women for the:

- management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids). (1.1, 14.1)
- management of moderate to severe pain associated with endometriosis. (1.2, 14.2)

Limitations of Use
Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss which may not be reversible. (1.3, 5.2, 6)

----------DOSAGE AND ADMINISTRATION----------

- Exclude pregnancy and discontinue hormonal contraceptives prior to MYFEMBREE initiation. (2.1)
- Take one tablet orally once daily. (2.2)
- 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. (2.3)
- If concomitant use of oral P-gp inhibitors is unavoidable, take MYFEMBREE at least 6 hours before taking the P-gp inhibitor (2.4)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: fixed-dose combination containing relugolix 40 mg, estradiol 1 mg and norethindrone acetate 0.5 mg. (3)

----------CONTRAINDICATIONS----------

- High risk of arterial, venous thrombotic, or thromboembolic disorder. (4)
- Pregnancy. (4)
- Known osteoporosis. (4)
- Current or history of breast cancer or other hormone-sensitive malignancies. (4)
- Known hepatic impairment or disease. (4)
- Undiagnosed abnormal uterine bleeding. (4)
- Known hypersensitivity to components of MYFEMBREE. (4)

----------WARNINGS AND PRECAUTIONS----------

- Thromboembolic Disorders and Vascular Events: Discontinue MYFEMBREE if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs. Discontinue MYFEMBREE if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis immediately. (5.1)
- Bone Loss: Decreases in bone mineral density (BMD) may not be completely reversible. Baseline BMD assessment is recommended in all women. In women with heavy menstrual bleeding associated with uterine fibroids, periodic BMD assessments are recommended. In women with moderate to severe pain associated with endometriosis, annual BMD assessments are recommended. Assess risk-benefit for women with additional risk factors for bone loss. (5.2)
- Suicidal Ideation and Mood Disorders (Including Depression): Advise patients to seek medical attention for new onset or worsening depression, anxiety, or other mood changes. (5.4)
- Hepatic Impairment and Transaminase Elevations: Counsel patients on signs and symptoms of liver injury. (5.5)
- 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. (5.7)
- 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. (5.8)
- Risk of Early Pregnancy Loss: Can cause early pregnancy loss. Advise women to use effective non-hormonal contraception. (5.9)
- Uterine Fibroid Prolapse or Expulsion: Advise patients to seek medical attention for severe uterine bleeding. (5.10)
- Hypersensitivity Reactions: Immediately discontinue MYFEMBREE if a hypersensitivity reaction occurs. (5.14)

----------ADVERSE REACTIONS----------

In women with heavy menstrual bleeding associated with uterine fibroids, most common adverse reactions (incidence ≥ 3%) are vasomotor symptoms, uterine bleeding, alopecia, and decreased libido.

In women with moderate to severe pain associated with endometriosis, most common adverse reactions (incidence ≥ 3%) are headache, vasomotor symptoms, mood disorders, abnormal uterine bleeding, nausea, toothache, back pain, decreased sexual desire and arousal, arthralgia, fatigue, and dizziness. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sumitomo Pharma America at 1-833-696-8268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Avoid use of MYFEMBREE with oral P-gp inhibitors. (7.1)
- Avoid use with combined P-gp and strong CYP3A inducers, as the exposure of the components of MYFEMBREE may be decreased. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Lactation: Advise women not to breastfeed while taking MYFEMBREE. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 04/2024

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FULL PRESCRIBING INFORMATION

WARNING: 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 (MI), especially in women at increased risk for these events *[see Warnings and Precautions (5.1)]*.**
- **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 *[see Contraindications (4)]*.**

1 INDICATIONS AND USAGE

1.1 Heavy Menstrual Bleeding Associated with Uterine Leiomyomas

MYFEMBREE is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women [*see Clinical Studies (14)*].

1.2 Moderate to Severe Pain Associated with Endometriosis

MYFEMBREE is indicated for the management of moderate to severe pain associated with endometriosis in premenopausal women [*see Clinical Studies (14)*].

1.3 Limitations of Use

Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss that may not be reversible *[see Warnings and Precautions (5.2) and Adverse Reactions (6)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of MYFEMBREE

- Exclude pregnancy *[see Contraindications (4)]*.
- Discontinue hormonal contraceptives *[see Warnings and Precautions (5.8)]*.

2.2 Recommended Dosage

- Take one tablet of MYFEMBREE orally once daily at approximately the same time, with or without food *[see Clinical Pharmacology (12.3)]*.
- Start MYFEMBREE as early as possible after the onset of menses but no later than seven days after menses has started [*see Clinical Studies (14)*].

- The recommended total duration of treatment with MYFEMBREE is 24 months *[see Indications and Usage (1.3), Warnings and Precautions (5.2), and Adverse Reactions (6)]*.

2.3 Missed Dose

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.

2.4 Dosage Modification for Concomitant Use with P-gp Inhibitors

Avoid concomitant use of MYFEMBREE with oral P-gp inhibitors. If concomitant use is unavoidable, take MYFEMBREE first and separate dosing by at least 6 hours *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: Each tablet of MYFEMBREE contains a fixed-dose combination of relugolix 40 mg, estradiol (E2) 1 mg, and norethindrone acetate (NETA) 0.5 mg. The tablets are light yellow to yellow, round, film-coated, and debossed with “MVT” on one side and “415” on the other side.

4 CONTRAINDICATIONS

MYFEMBREE is contraindicated in women:

- With a high risk of arterial, venous thrombotic, or thromboembolic disorders *[see Boxed Warning and Warnings and Precautions (5.1)]*. 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 (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular disease)
  - thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
  - inherited or acquired hypercoagulopathies
  - uncontrolled hypertension
  - headaches with focal neurological symptoms or migraine headaches with aura if over 35 years of age
- Who are pregnant. Exposure to MYFEMBREE early in pregnancy may increase the risk of early pregnancy loss *[see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)]*.
- With known osteoporosis, because of the risk of further bone loss *[see Warnings and Precautions (5.2)]*.
- With current or history of breast cancer or other hormone-sensitive malignancies, and with increased risk for hormone-sensitive malignancies *[see Warnings and Precautions (5.3)]*.
- With known hepatic impairment or disease *[see Warnings and Precautions (5.5)]*.
- With undiagnosed abnormal uterine bleeding.
- With known anaphylactic reaction, angioedema, or hypersensitivity to MYFEMBREE or any of its components. Anaphylactoid reactions, urticaria, and angioedema have been reported *[see Warnings and Precautions (5.14), Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Thromboembolic Disorders and Vascular Events

MYFEMBREE is contraindicated in women with current or history of thrombotic or thromboembolic disorders and in women at increased risk for these events *[see Contraindications (4)]*.

Discontinue MYFEMBREE immediately if an arterial or venous thrombotic, cardiovascular, or cerebrovascular event occurs or is suspected. Discontinue MYFEMBREE at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization, if feasible.

Discontinue MYFEMBREE immediately if there is sudden unexplained partial or complete loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions and evaluate for retinal vein thrombosis as these have been reported in patients receiving estrogens and progestins.

Estrogen and progestin combinations, including the estradiol/norethindrone acetate component of MYFEMBREE, increase the risk of thrombotic or thromboembolic disorders, including pulmonary embolism, deep vein thrombosis, stroke, and myocardial infarction, especially in women at high risk for these events. In general, the risk is greatest among women over 35 years of age who smoke and women with uncontrolled hypertension, dyslipidemia, vascular disease, or obesity.

Two thromboembolic events (DVT and PE) occurred in one woman treated for 38 days with MYFEMBREE for moderate to severe pain associated with endometriosis.

5.2 Bone Loss

MYFEMBREE is contraindicated in women with known osteoporosis *[see Contraindications (4)]*. 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 bone mineral density (BMD) (e.g., systemic or chronic inhaled corticosteroids, anticonvulsants, or chronic use of proton pump inhibitors).

Assessment of BMD by dual-energy X-ray absorptiometry (DXA) is recommended at baseline. In women with heavy menstrual bleeding associated with uterine fibroids, periodic DXA during treatment with MYFEMBREE is recommended. In women with moderate to severe pain associated with endometriosis, annual DXA is recommended while taking MYFEMBREE. Consider discontinuing MYFEMBREE if the risk associated with bone loss exceeds the potential benefit of treatment. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation for patients with inadequate dietary intake may be beneficial. MYFEMBREE may cause a decrease in BMD in some patients. BMD loss may be greater with increasing duration of use and may not be completely reversible after stopping treatment *[see Adverse Reactions (6.1)]*. The impact of BMD decreases on long-term bone health and future fracture risk in premenopausal women is unknown.

5.3 Hormone-Sensitive Malignancies

MYFEMBREE is contraindicated in women with current or a history of hormone-sensitive malignancies (e.g., breast cancer) and in women at increased risk for hormone-sensitive malignancies *[see Contraindications (4)]*. Discontinue MYFEMBREE if a hormone-sensitive malignancy is diagnosed.

Surveillance measures in accordance with standard of care, such as breast examinations and mammography, are recommended. The use of estrogen alone or estrogen plus progestin has been reported to result in an increase in abnormal mammograms requiring further evaluation.

5.4 Suicidal Ideation and Mood Disorders (Including Depression)

Evaluate patients with a history of suicidal ideation, depression, and mood disorders prior to initiating treatment. Monitor patients for mood changes and depressive symptoms including shortly after initiating treatment, to determine whether the risks of continuing therapy with MYFEMBREE outweigh the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Re-evaluate the benefits and risks of continuing MYFEMBREE if such events occur.

Gonadotropin-releasing hormone receptor antagonists, including MYFEMBREE, have been associated with mood disorders (including depression) and suicidal ideation.

In Studies L1 and L2 in women with heavy menstrual bleeding associated with uterine fibroids, a greater proportion of women treated with MYFEMBREE compared with placebo reported depression (including depression, mood swings, and depressed mood) (2.4% vs. 0.8%), irritability (2.4% vs. 0%), and anxiety (1.2% vs. 0.8%) *[see Adverse Reactions (6.1)]*.

In Studies S1 and S2 in women with moderate to severe pain associated with endometriosis, a greater proportion of women treated with MYFEMBREE as compared to placebo reported mood disorders (including depression) (9.1% vs. 7.2%). In addition, cases of suicidal ideation were reported with MYFEMBREE use. All women who reported suicidal ideation had a history of depression and/or anxiety *[see Adverse Reactions (6.1)]*.

5.5 Hepatic Impairment and Transaminase Elevations

Contraindication in Patients with Hepatic Impairment

MYFEMBREE is contraindicated in patients with known hepatic impairment or disease *[see Contraindications (4) and Use in Specific Populations (8.6)]*. Steroid hormones may be poorly metabolized in patients with impaired liver function *[see Clinical Pharmacology (12.3)]*.

Transaminase Elevations

Instruct women to promptly seek medical attention for symptoms or signs that may reflect liver injury, such as jaundice or right upper abdominal pain. Acute liver test abnormalities may necessitate the

discontinuation of MYFEMBREE use until the liver tests return to normal and MYFEMBREE causation has been excluded.

In placebo-controlled clinical trials, in women with uterine fibroids or endometriosis, elevations (≥ 3 times the upper limit of the normal [ULN] of reference range) in alanine aminotransferase (ALT) occurred in 0.4% (1/254) and 0.7% (3/418) of MYFEMBREE-treated women, respectively, as compared to 0% (0/256) and 0.5% (2/416) of placebo-treated women, respectively; moreover, elevations (≥ 3 times ULN of reference range) in aspartate aminotransferase (AST) occurred in 0.8% (2/254) and 0.2% (1/418) of MYFEMBREE-treated women, respectively, as compared to 0.4% (1/256) and 0.5% (2/416) of placebo-treated women, respectively. No patterns in time to onset of these liver transaminase elevations were identified.

5.6 Gallbladder Disease or History of Cholestatic Jaundice

Discontinue MYFEMBREE if signs or symptoms of gallbladder disease or jaundice occur. For women with a history of cholestatic jaundice associated with past estrogen use or with pregnancy, assess the risk-benefit of continuing therapy. Studies among estrogen users suggest a small increased relative risk of developing gallbladder disease.

5.7 Elevated Blood Pressure

MYFEMBREE is contraindicated in women with uncontrolled hypertension *[see Contraindications (4)]*. For women with well-controlled hypertension, continue to monitor blood pressure and stop MYFEMBREE if blood pressure rises significantly.

In the placebo-controlled clinical trials in women with heavy menstrual bleeding associated with uterine fibroids or with moderate to severe pain associated with endometriosis, more women in one study (Study L1; uterine fibroids) experienced the adverse reaction of new or worsening hypertension with MYFEMBREE compared to placebo (7.0% vs. 0.8%).

5.8 Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

Exclude pregnancy before initiating MYFEMBREE *[see Dosage and Administration (2.1)]*. Start MYFEMBREE as early as possible after the start of menses but no later than 7 days after menses has started. If MYFEMBREE is initiated later in the menstrual cycle, irregular and/or heavy bleeding may initially occur. Women who take MYFEMBREE may experience amenorrhea or a reduction in the amount, intensity, or duration of menstrual bleeding, which may delay the ability to recognize pregnancy. Perform pregnancy testing if pregnancy is suspected and discontinue MYFEMBREE if pregnancy is confirmed *[see Use in Specific Populations (8.1, 8.3)]*.

Advise women of reproductive potential to use effective non-hormonal contraception during treatment with MYFEMBREE and for one week after the final dose. Avoid concomitant use of hormonal contraceptives with MYFEMBREE. The use of estrogen-containing hormonal contraceptives can increase estrogen levels which may increase the risk of estrogen-associated adverse events and decrease the efficacy of MYFEMBREE *[see Use in Specific Populations (8.1, 8.3)]*.

5.9 Risk of Early Pregnancy Loss

MYFEMBREE is contraindicated for use in pregnancy *[see Contraindications (4)]*. Based on findings from animal studies and its mechanism of action, MYFEMBREE can cause early pregnancy loss. However, in both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures about half and approximately 300 times exposures in women at the recommended human dose *[see Use in Specific Populations (8.1)]*.

5.10 Uterine Fibroid Prolapse or Expulsion

Advise women with known or suspected submucosal uterine fibroids about the possibility of uterine fibroid prolapse or expulsion and instruct them to contact their physician if severe bleeding and/or cramping occurs while being treated with MYFEMBREE. In Studies L1 and L2, uterine fibroid prolapse or uterine fibroid expulsion were reported in women treated with MYFEMBREE *[see Adverse Reactions (6.1)]*.

5.11 Alopecia

Consider discontinuing MYFEMBREE if hair loss becomes a concern *[see Adverse Reactions (6.1)]*.

In Phase 3 placebo-controlled clinical trials in women with heavy menstrual bleeding associated with uterine fibroids, 3.5% of MYFEMBREE-treated women experienced alopecia, hair loss, and hair thinning as compared to 0.8% of placebo-treated women. In 3 of the 11 affected women treated with MYFEMBREE across Studies L1 and L2, alopecia was reported as moderate. For one MYFEMBREE-treated woman in the extension trial, alopecia was a reason for discontinuing treatment. No specific pattern of hair loss was described. The majority of affected women completed the study with reported hair loss ongoing. Whether the hair loss is reversible is unknown *[see Adverse Reactions (6.1)]*.

5.12 Effects on Carbohydrate and Lipid Metabolism

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 MYFEMBREE if hypercholesterolemia or hypertriglyceridemia worsens. In women with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations in triglycerides levels leading to pancreatitis. Use of MYFEMBREE is associated with increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C) *[see Adverse Reactions (6.1)]*.

5.13 Effect on Other Laboratory Results

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 (e.g., thyroid-binding globulin, corticosteroid-binding globulin), 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 *[see Clinical Pharmacology (12.2)]*.

5.14 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactoid reactions, urticaria and angioedema, have been reported with MYFEMBREE *[see Adverse Reactions (6.2)]*. MYFEMBREE is contraindicated in women with a history of hypersensitivity reactions to relugolix or any component of MYFEMBREE *[see Contraindications (4)]*. Immediately discontinue MYFEMBREE if a hypersensitivity reaction occurs.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed elsewhere in the labeling:

- Thromboembolic Disorders and Vascular Events *[see Warnings and Precautions (5.1)]*
- Bone Loss *[see Warnings and Precautions (5.2)]*
- Suicidal Ideation and Mood Disorders (Including Depression) *[see Warnings and Precautions (5.4)]*
- Hepatic Impairment and Transaminase Elevations *[see Warnings and Precautions (5.5)]*
- Elevated Blood Pressure *[see Warnings and Precautions (5.7)]*
- Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy *[see Warnings and Precautions (5.8)]*
- Uterine Fibroid Prolapse or Expulsion *[see Warnings and Precautions (5.10)]*
- Alopecia *[see Warnings and Precautions (5.11)]*
- Effects on Carbohydrate and Lipid Metabolism *[see Warnings and Precautions (5.12)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.14)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

<u>Heavy Menstrual Bleeding Associated with Uterine Leiomyomas</u>

The safety of MYFEMBREE was evaluated in two placebo-controlled clinical trials, Study L1 (LIBERTY 1) and Study L2 (LIBERTY 2), in women with heavy menstrual bleeding associated with uterine fibroids. In these trials, women received a once daily relugolix 40-mg tablet and an over-encapsulated tablet of E2 1 mg and NETA 0.5 mg (relugolix + E2/NETA), which is equivalent to 1 tablet of MYFEMBREE. Across the two trials, 254 women received MYFEMBREE once daily for 24 weeks. Additionally, 256 women received placebo for 24 weeks, and 258 women received relugolix 40-mg monotherapy once daily for 12 weeks followed by MYFEMBREE for 12 weeks *[see Clinical*

Studies (14.1)]. Of these, 476 women were treated with MYFEMBREE in a 28-week extension trial, Study L3 (LIBERTY Extension), for a total treatment duration of up to 12 months. Demographics were similar across the studies; approximately 43% were White, 51% were Black, and approximately 23% were of Hispanic or Latino ethnicity. The mean age at study entry was approximately 42 years (range 19 to 51 years). Of women who completed Study L3, 229 were rerandomized to continue MYFEMBREE or withdraw from therapy (placebo) for an additional 52 weeks (Study L4).

Serious Adverse Reactions

In Studies L1 and L2, serious adverse reactions were reported in 3.1% of MYFEMBREE-treated women as compared to 2.3% of placebo-treated women. In MYFEMBREE-treated women, serious adverse drug reactions included uterine myoma expulsion and menorrhagia experienced by one woman and uterine leiomyoma (prolapse), cholecystitis, and pelvic pain reported for one woman each.

Adverse Reactions Leading to Study Drug Discontinuation

In Studies L1 and L2, 3.9% of women treated with MYFEMBREE discontinued therapy due to adverse reactions, as compared to 4.3% receiving placebo. The most common adverse reaction leading to discontinuation of MYFEMBREE was uterine bleeding (1.2%) with an onset usually reported within the first 3 months of therapy.

Common Adverse Reactions

The most common adverse reactions reported in at least 3% of women treated with MYFEMBREE for heavy menstrual bleeding associated with uterine fibroids and at an incidence greater than placebo during double-blind placebo-controlled treatment are summarized below in Table 1.

Table 1: Adverse Reactions Occurring in 3% or More in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids Treated with MYFEMBREE in Studies L1 and L2

Adverse Reaction	MYFEMBREE (N = 254) %	Placebo (N = 256) %
Vasomotor symptoms[1]	10.6	6.6
Abnormal uterine bleeding[2]	6.3	1.2
Alopecia	3.5	0.8
Libido decreased[3]	3.1	0.4

[1] Includes hot flush, hyperhidrosis, or night sweats.
[2] Includes menorrhagia, metrorrhagia, vaginal hemorrhage, polymenorrhea, and menstruation irregular.
[3] Includes libido decreased and loss of libido.

In Study L1, more women experienced the adverse reaction of new or worsening hypertension with MYFEMBREE as compared to placebo (7.0% vs. 0.8%).

The most common adverse reactions reported during the extension trial, Study L3, were similar to those reported in the placebo-controlled trials.

Less Common Adverse Reactions

Adverse reactions reported in at least 2% and less than 3% of women with heavy menstrual bleeding associated with uterine fibroids in the MYFEMBREE treated group and greater incidence than placebo included irritability, dyspepsia, and breast cyst. Other important adverse reactions reported in MYFEMBREE-treated women included one serious reaction each of uterine myoma expulsion (0.4%) and uterine leiomyoma (prolapse) (0.4%).

Bone Loss

The effect of MYFEMBREE on BMD was assessed by DXA. The least squares mean percent changes from baseline in lumbar spine BMD at Month 6 in Studies L1 and L2 are presented below in Table 2.

Table 2: Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids in Studies L1 and L2 at Month 6

	MYFEMBREE	**Placebo**
Number of subjects	254	256
Percent change from baseline (95% CI)	-0.23 (-0.64, 0.18)	0.18 (-0.21, 0.58)
Treatment difference, %	-0.42	

Abbreviations: BMD = bone mineral density; CI = confidence interval.

In the open-label extension trial, Study L3, women received an additional 28 weeks of MYFEMBREE for a total of up to 52 weeks of treatment. Women from Study L3 showed continued bone loss at Months 6 and 12 when treated with up to 52 weeks of MYFEMBREE. The least squares mean percent changes from baseline in lumbar spine BMD at Months 6 and 12 are presented below in Table 3.

Table 3: Mean Percent Change (On-Treatment) from Baseline* in Lumbar Spine BMD at Month 6* and Month 12 for MYFEMBREE-Treated Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids in Study L3

	Number of Women (N = 163)	
	Month 6*	**Month 12**
Percent change from baseline* (95% CI)	-0.23 (-0.69, 0.24)	-0.80 (-1.36, -0.25)

Abbreviations: BMD = bone mineral density; CI = confidence interval.
* Baseline and Month 6 assessments include only those participants from Studies L1 and L2 who participated in Study L3.

A separate concurrent prospective observational study enrolled 262 women with heavy menstrual bleeding associated with uterine fibroids who were age-matched to participants of Studies L1 and L2. While these women were not randomized to receive treatment for heavy menstrual bleeding associated with uterine fibroids, women were permitted to receive treatment from their provider during the clinical trials for this indication. Women underwent DXA scans at baseline, Month 6 and Month 12 to monitor for changes in BMD. The mean percent changes from baseline (95% CI) in lumbar spine BMD at Months 6 and 12 were 0.00 (-0.32, 0.31) and -0.41 (-0.77, -0.05), respectively.

A decline in lumbar spine BMD of > 3% was observed in 23% (30/132) of women who had a DXA scan following 12 months of MYFEMBREE treatment in Study L3 and in 17.4% (37/213) of untreated women in the Observational Uterine Fibroids Cohort. A decline of > 8% was seen in 0.8% (1/132) of women treated with MYFEMBREE who completed a DXA scan at Month 12 and in 0.9% (2/213) of untreated women in the Observational Uterine Fibroids Cohort.

In Studies L1, L2, and L3, four of women treated with MYFEMBREE experienced low trauma fractures (defined as a fall from standing height or less). Two women, one from Study L1 and one from Study L2, fractured after 117 and 166 days of treatment with MYFEMBREE. Two women in Study L3, both treated with relugolix monotherapy for 12 weeks prior to MYFEMBREE therapy, fractured after 149 and 164 days of treatment with MYFEMBREE.

Depression, Mood Disorders, and Suicidal Ideation

In Studies L1 and L2, MYFEMBREE was associated with adverse mood changes. A greater proportion of women treated with MYFEMBREE compared to placebo reported depression (including depression, mood swings, and depressed mood) (2.4% vs. 0.8%), irritability (2.4% vs. 0%), and anxiety (1.2% vs. 0.8%).

Resumption of Menstruation after Discontinuation

Post study menstrual status was available for 35 women in Study L1 and 30 women in Study L2 who were treated with MYFEMBREE and prematurely discontinued the study or did not continue into the long-term extension study. For these women, 100% (35/35) in Study L1 and 93.3% (28/30) in Study L2 resumed menses. The mean time from last dose to occurrence of menses was 36 days in Study L1 and 30.7 days in Study L2. Mean time to occurrence of menses was longer for women who achieved amenorrhea (40.6 days and 41.1 days in Studies L1 and L2, respectively) compared with women without amenorrhea (33.0 days and 26.6 days in Studies L1 and L2, respectively) in the last 35 days of treatment. After 12 months of treatment with MYFEMBREE (Study L1 or Study L2, then Study L3) 93.8% (61/65) of women resumed menses. Mean time from last dose of drug to occurrence of menses was 40.5 days. Mean time to occurrence of menses was longer in women who reported amenorrhea over the last 35 days of treatment compared with women without amenorrhea over the last 35 days of treatment (45.6 days vs. 32.6 days, respectively).

Women who did not have a return to menses included those who had surgery, used alternative medications associated with amenorrhea, entered menopause, and unknown cause.

Increases in Lipids

Lipid levels were assessed at baseline and Week 24/End of Treatment in Studies L1 and L2. Among women with normal total cholesterol (< 200 mg/dL) at baseline, increases to 200 to < 240 mg/dL were seen in 13.7% of women treated with MYFEMBREE as compared to 7.7% of women treated with placebo, and increases to ≥ 240 mg/dL were seen in 1.7% and 0.6% of MYFEMBREE- and placebo-treated women, respectively. For women with LDL < 130 mg/dL at baseline, increases to 130 to < 160 mg/dL, 160 to < 190 mg/dL and ≥ 190 mg/dL were seen in 9.3%, 1.5%, and 0.5% of women treated with MYFEMBREE as compared to 6.5%, 0.5% and 0% of women treated with placebo, respectively.

Moderate to Severe Pain Associated with Endometriosis

The safety of MYFEMBREE was evaluated in two placebo-controlled clinical trials, Study S1 and Study S2, in women with moderate to severe pain associated with endometriosis. In these trials, women received once daily one relugolix 40-mg tablet with one over-encapsulated tablet of E2 1 mg and NETA 0.5 mg (relugolix + E2/NETA), which is equivalent to one tablet of MYFEMBREE. Across the two trials, 418 women received MYFEMBREE once daily for 24 weeks, 416 women received placebo for 24 weeks, and 417 women received relugolix 40 mg monotherapy once daily for 12 weeks followed by MYFEMBREE for 12 weeks *[see Clinical Studies (14)]*. Of these, 799 women were treated with MYFEMBREE in an 80-week extension trial, Study S3, for a total treatment duration of up to 24 months. Demographics were similar across these trials; 91% were white, 6% were Black, and 12% were of Hispanic or Latino ethnicity. The mean age at study entry was 34 years (range 18 to 50 years).

Serious Adverse Reactions

In Studies S1 and S2, serious adverse reactions were reported in 2.9% of MYFEMBREE-treated women as compared to 2.2% of placebo-treated women. In MYFEMBREE-treated women, serious adverse reactions included uterine hemorrhage, suicidal ideation, cholelithiasis, and cholecystitis.

Adverse Reactions Leading to Study Drug Discontinuation

In Studies S1 and S2, 4.5% of MYFEMBREE-treated women discontinued therapy due to adverse reactions as compared to 2.9% of placebo-treated women. The most common adverse reaction (1.7%) leading to discontinuation in MYFEMBREE-treated women was mood-related disorders (including depression, mood swings, altered mood, affect lability, and suicidal ideation).

Common Adverse Reactions

The most common adverse reactions reported in at least 3% of women treated with MYFEMBREE for moderate to severe pain associated with endometriosis and with an incidence greater than placebo during Studies S1 and S2 are summarized below in Table 4.

Table 4: Adverse Reactions Occurring in 3% or More of Women with Moderate to Severe Pain Associated with Endometriosis Treated with MYFEMBREE

Adverse Reaction	MYFEMBREE (N = 418) %	Placebo (N = 416) %
Headache	33.0	26.4
Vasomotor symptoms[1]	13.2	7.2
Mood disorders[2]	9.1	7.2
Abnormal uterine bleeding[3]	6.7	4.6
Nausea	6.0	4.1
Toothache	5.5	2.4
Back pain	4.8	2.9
Decreased sexual desire and arousal[4]	4.3	1.2
Arthralgia	3.6	2.2
Fatigue	3.1	2.4
Dizziness	3.1	1.2

[1] Includes hot flush, hyperhidrosis, night sweats, and flushing.
[2] Includes affect lability, affective disorder, anxiety, depressed mood, depression, emotional distress, generalized anxiety disorder, irritability, mixed anxiety and depressive disorder, mood altered, mood swings, and suicidal ideation.
[3] Includes menorrhagia, metrorrhagia, vaginal hemorrhage, uterine hemorrhage, polymenorrhea, and menstruation irregular.
[4] Includes libido decreased, libido disorder, and female sexual arousal disorder.

The most common adverse reactions reported in the safety extension trial, Study S3, were similar to those reported in the placebo-controlled trials.

Less Common Adverse Reactions

Adverse reactions reported in at least 2% and less than 3% of women with moderate to severe pain associated with endometriosis in the MYFEMBREE group and with a greater incidence than placebo included diarrhea (2.4%), peripheral edema (2.2%), and vulvovaginal dryness (2.2%).

Bone Loss

The effect of MYFEMBREE on BMD was assessed by DXA. The least squares (LS) mean percent changes from baseline in lumbar spine BMD at Month 6 and for women with moderate to severe pain associated with endometriosis in Studies S1 and S2 are presented in Table 5.

Table 5: LS Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in Women with Moderate to Severe Pain Associated with Endometriosis at Month 6 in Studies S1 and S2

	Treatment Month 6	
	MYFEMBREE	**Placebo**
Number of subjects	418	416
Percent change from baseline (95% CI)	-0.72 (-1.06, -0.38)	0.12 (-0.22, 0.47)
Treatment difference, %	-0.84	

Abbreviations: LS = least squares; BMD = bone mineral density; CI = confidence interval.

In the open-label extension, Study S3, women received an additional 80 weeks of MYFEMBREE for a total of up to 24 months of treatment. The least squares (LS) mean percent changes from baseline in lumbar spine BMD at Months 6, 12, and 24 for women treated with MYFEMBREE in Studies S1 and S2 and then continued MYFEMBREE for an additional 80 weeks in Study S3 are presented below in Table 6.

Table 6: LS Mean Percent Change (On-Treatment) from Baseline* in Lumbar Spine BMD at Months 6*, 12, and 24 for Women with Moderate to Severe Pain Associated with Endometriosis Treated with MYFEMBREE in Study S3

	Number of Women (N = 277)		
	Month 6* (n=264)	**Month 12 (n=228)**	**Month 24 (n=163)**
Percent change from baseline* (95% CI)	-0.91 (-1.30, -0.53)	-0.81 (-1.26, -0.36)	-0.45 (-1.03, 0.13)

Abbreviations: LS = least squares; BMD = bone mineral density; CI = confidence interval; N = number of subjects who received continuous MYFEMBREE treatment throughout Studies S1/S2 and S3; n = number of subjects who had BMD assessments.
* Baseline and Month 6 assessments include only those participants from Studies S1 and S2 who also participated in Study S3.

Changes in bone mineral density with MYFEMBREE treatment beyond 24 months have not been elucidated.

A separate concurrent prospective observational study enrolled 452 women with moderate to severe pain associated with endometriosis who were age-matched to participants of Studies S1 and S2. While these women were not randomized to receive treatment for moderate to severe pain associated with endometriosis, women were permitted to receive treatment from their provider for this indication. Women underwent DXA scans at baseline and Months 6 and 12 to monitor for changes in BMD. The mean percent changes from baseline (95% CI) in lumbar spine BMD at Months 6 and 12 were 0.35 (0.13, 0.57) and 0.53 (0.24, 0.83), respectively.

In women with moderate to severe pain associated with endometriosis, a decline in lumbar spine BMD of > 3% from pre-treatment baseline was observed in 19.7% (45/228) of women who had a DXA scan following 12 months of MYFEMBREE treatment in Study S3 and in 9.1% (29/320) of untreated women in the Observational Endometriosis Cohort. A decline of > 7% to ≤ 8% from pre-treatment baseline was seen in 0.9% (2/228) of women treated with MYFEMBREE who completed a DXA scan at Month 12 in Study S3 and in 0.6% (2/320) of untreated women in the Observational Endometriosis Cohort.

Following 24 months of MYFEMBREE treatment in Study S3, a decline in lumbar spine BMD of > 3% from pre-treatment baseline occurred in 20.2% (33/163) of women and a decline of > 7% from pre-treatment baseline occurred in 2.5% (4/163) of women. At the femoral neck, a decline in BMD of >7% was observed in 1.8% (3/163) women, one of whom (0.6%) also had a decline in BMD of > 7% at the total hip. The maximum percent decline from pre-treatment baseline at the lumbar spine, femoral neck and total hip at Month 24 was 9.1%, 8.8% and 7.0%, respectively.

BMD loss may not be completely reversible after stopping treatment.

In Study S3, two women sustained fractures after falling. One woman, who was treated for almost 24 weeks with MYFEMBREE following 12 weeks of relugolix monotherapy, sustained a tibia/fibula fracture and one who was treated for 104 weeks with MYFEMBREE, sustained a wrist fracture 144 days after she discontinued MYFEMBREE. The impact of BMD loss on long-term bone health and future fracture risk in premenopausal women is unknown.

Suicidal Ideation and Mood Disorders (Including Depression)

In Studies S1 and S2, a greater proportion of women treated with MYFEMBREE compared with placebo reported mood disorders (including depression) (9.1% vs. 7.2%).

In addition, cases of suicidal ideation were reported in the safety extension trial, Study S3.

Resumption of Menstruation after Discontinuation

Post-study menstrual status was available for 55 women in Study S1 and 59 women in Study S2 who were treated with MYFEMBREE and either prematurely discontinued the study or did not continue into the extension study. For these women, 83.6% (46/55) in Study S1 and 84.7% (50/59) in Study S2 resumed menses. The mean time from last dose to occurrence of menses was 27.1 days in Study S1 and 39.2 days in Study S2. Mean time to occurrence of menses was longer for women who achieved amenorrhea (34.3 days and 42.8 days in Studies S1 and S2, respectively) compared with women without amenorrhea (21.0 days and 32.1 days in Studies S1 and S2, respectively) in the last 28 days of treatment. After 12 months of treatment with MYFEMBREE (Study S1 or Study S2, then Study S3), 97.9%

(46/47) of women resumed menses. Mean time from last dose of drug to occurrence of menses was 36.7 days.

Women who did not have a return to menses included those who had surgery, used alternative medications associated with amenorrhea, or became pregnant.

Increases in Lipids

Lipid levels were assessed at baseline and Week 24/End of Treatment in Studies S1 and S2. Among women with normal total cholesterol (< 200 mg/dL) at baseline, increases to ≥ 200 to < 240 mg/dL were seen in 13.6% (41/302) of MYFEMBREE- treated women as compared to 9.3% (27/289) of placebo-treated women, and increases to ≥ 240 mg/dL were seen in 0.7% (2/302) of MYFEMBREE-treated women as compared to 1.0% (3/289) of placebo-treated women. For women with LDL < 130 mg/dL at baseline, increases to 130 to < 160 mg/dL, 160 to < 190 mg/dL and ≥ 190 mg/dL were seen in 8.0%, 0.3%, and 0% of MYFEMBREE-treated women as compared to 7.6%, 0% and 0% of placebo-treated women. Among women with normal HDL at baseline (≥ 60 mg/dL), declines to 40 to < 60 mg/dL occurred in 22.2% (49/221) of MYFEMBREE-treated women as compared to 12.2% (27/221) of placebo-treated women.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of MYFEMBREE, as well as post-approval use of relugolix monotherapy outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: anaphylactoid reaction
Skin and subcutaneous tissue disorders: drug eruption, angioedema, urticaria
Neoplasms (benign, malignant, and unspecified): uterine leiomyoma degeneration

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on MYFEMBREE

P-gp Inhibitors

Co-administration of MYFEMBREE with P-gp inhibitors increases the AUC and maximum concentration (C_{max}) of relugolix *[see Clinical Pharmacology (12.3)]* 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 *[see Dosage and Administration (2.4)]*.

Combined P-gp and Strong CYP3A Inducers

Use of MYFEMBREE with combined P-gp and strong CYP3A inducers decreases the AUC and C_{max} of relugolix, estradiol, and/or norethindrone *[see Clinical Pharmacology (12.3)]* and may decrease the therapeutic effects of MYFEMBREE. Avoid use of MYFEMBREE with combined P-gp and strong CYP3A inducers.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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.

Risk Summary

MYFEMBREE is contraindicated in pregnancy *[see Contraindications (4) and Warnings and Precautions (5.9)]*. Based on findings from animal studies and its mechanism of action, MYFEMBREE may cause early pregnancy loss. Discontinue MYFEMBREE if pregnancy occurs during treatment *[see Warnings and Precautions (5.9) and Clinical Pharmacology (12.1)]*.

The limited human data with the use of MYFEMBREE in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *[see Data]*.

In animal reproduction studies, oral administration of relugolix in pregnant rabbits during organogenesis resulted in spontaneous abortion and total litter loss at relugolix exposures about half those at the maximum recommended human dose (MRHD) of 40 mg. In both rabbits and rats, no fetal malformations were present at any dose level tested which were associated with relugolix exposures about half and approximately 300 times exposures in women at the MRHD, respectively *[see Data]*.

Epidemiologic studies and meta-analyses have not found an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following exposure to estrogens and progestins before conception or during early pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. There are insufficient data to conclude whether the presence of uterine fibroids or endometriosis reduces the likelihood of achieving pregnancy or increases the risk of adverse pregnancy outcomes. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum recommended human dose [MRHD] of 40 mg daily, based on AUC). No treatment related malformations were observed in surviving fetuses. No treatment related effects were observed at 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH receptors is unknown.

In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no observed adverse effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for GnRH receptors is more than 1000-fold lower than that in humans, and this study represents an assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related malformations were observed up to 1000 mg/kg/day.

In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD).

8.2 Lactation

Risk Summary

There are no data on the presence of relugolix or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Relugolix was detected in milk in lactating rats *[see Data]*. When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Detectable amounts of estrogen and progestin have been identified in the breast milk of women receiving estrogen plus progestin therapy and can reduce milk production in breast-feeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established.

The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for MYFEMBREE and any potential adverse effects on the breastfed child from MYFEMBREE or from the underlying maternal condition.

Data

Animal Data
In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Females and Males of Reproductive Potential

Based on animal data and the mechanism of action, MYFEMBREE can cause early pregnancy loss if MYFEMBREE is administered to pregnant women *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

MYFEMBREE may delay the ability to recognize pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding *[see Warnings and Precautions (5.8)]*. Exclude pregnancy before initiating treatment with MYFEMBREE. Perform pregnancy testing if pregnancy is suspected during treatment with MYFEMBREE and discontinue treatment if pregnancy is confirmed *[see Contraindications (4) and Warnings and Precautions (5.8)]*.

Contraception

Advise women of reproductive potential to use effective non-hormonal contraception during treatment with MYFEMBREE and for at least 1 week following discontinuation. Avoid concomitant use of hormonal contraceptives with MYFEMBREE. The use of estrogen-containing hormonal contraceptives may increase the risk of estrogen-associated adverse events and is expected to decrease the efficacy of MYFEMBREE *[see Warnings and Precautions (5.8)]*.

8.4 Pediatric Use

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

8.6 Hepatic Impairment

MYFEMBREE is contraindicated in women with hepatic impairment or disease *[see Contraindications (4)]*. The use of E2 (a component of MYFEMBREE) in patients with hepatic impairment is expected to increase the exposure to E2 and increase the risk of E2-associated adverse reactions *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdosage of estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness, fatigue, and withdrawal bleeding.

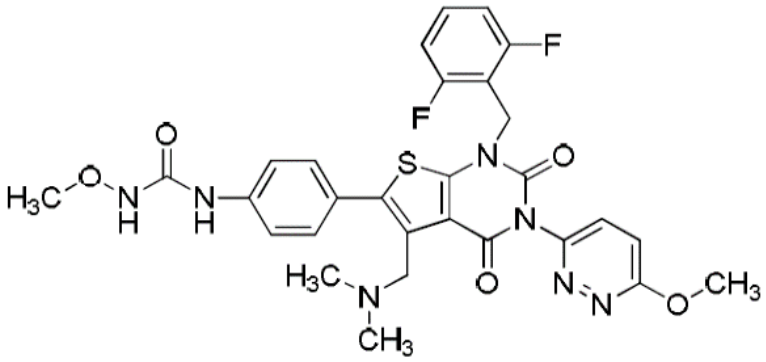
Supportive care is recommended if an overdose occurs. The amount of relugolix, estradiol, or norethindrone removed by hemodialysis is unknown.

11 DESCRIPTION

MYFEMBREE tablets for oral administration contain a fixed-dose combination of relugolix 40 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg as active ingredients.

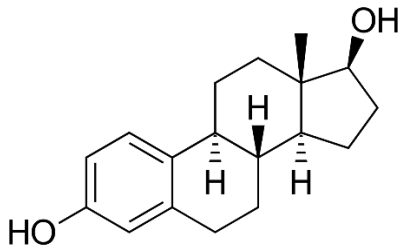
Relugolix is a non-peptide small molecule, GnRH receptor antagonist. It is a white to off white to slightly yellow solid and is sparingly soluble in water. The chemical name is N-(4-{1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxo-1,2,3,4-

tetrahydrothieno[2,3-d]pyrimidin-6-yl}phenyl)-N-methoxyurea with the empirical formula of $C_{29}H_{27}F_2N_7O_5S$ and a molecular weight of 623.63. The structural formula is:



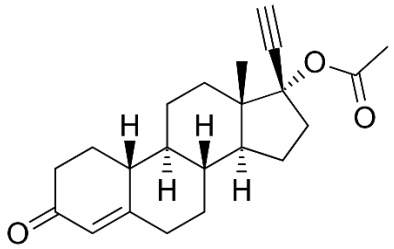
relugolix

Estradiol (E2), an estrogen, is present as the hemihydrate ($C_{18}H_{24}O_2$•½H_2O) which is a white or almost white crystalline powder. Its chemical name is estra-1, 3, 5 (10)-triene-3, 17β-diol with the empirical formula of $C_{18}H_{24}O_2$ and a molecular weight of 272.4. The structural formula is:



estradiol

Norethindrone acetate (NETA), a progestin, is a white or yellowish-white crystalline powder. Its chemical name is 17-Hydroxy-19-nor-17α-pregn-4-en-20-yn-3-one acetate with the empirical formula of $C_{22}H_{28}O_3$ and a molecular weight of 340.5. The structural formula is:



norethindrone acetate

Each MYFEMBREE (relugolix, estradiol, and norethindrone acetate) film-coated tablet contains the following inactive ingredients: hydroxypropyl cellulose, hypromellose, iron oxide yellow, lactose monohydrate, mannitol, magnesium stearate, sodium starch glycolate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism 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 and pain associated with endometriosis.

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.

12.2 Pharmacodynamics

Estradiol and norethindrone acetate (components of MYFEMBREE) may have the following effects:

- Increased thyroxin-binding globulin levels leading to *[see Warnings and Precautions (5.13)]:*
  - Increased circulating total thyroid hormone concentrations as measured by protein-bound iodine (PBI), thyroxine (T4) levels (by column or by radioimmunoassay), or triiodothyronine (T3) concentrations by radioimmunoassay
  - Decreased T3 resin uptake
  - Unaltered free T4 and free T3 concentrations in women with normal thyroid function *[see Warnings and Precautions (5.13)]*.
- Elevated corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG) concentrations leading to increases in total circulating corticosteroid and sex hormone concentrations, respectively *[see Warnings and Precautions (5.13)]*.
- Possible decreased free testosterone concentrations.
- Possible increased other plasma proteins concentrations (angiotensinogen/renin substrate, alpha-1 antitrypsin, ceruloplasmin).
- Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction concentration, reduced low-density lipoprotein concentration, increased triglyceride concentrations.
- Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time; increased platelet count; increased factors II, VII antigen, VIII coagulant activity, IX, X, XII,

VII-X complex, and beta-thromboglobulin; decreased concentrations of anti-factor Xa and antithrombin III, decreased antithrombin III activity, increased concentrations of fibrinogen and fibrinogen activity; increased plasminogen antigen and activity.

Cardiac Electrophysiology

At a dose 9 times the maximum approved recommended dose of relugolix, the QT interval was not prolonged to a clinically relevant extent.

The effect of estradiol and norethindrone acetate (two of the components of MYFEMBREE) on the QTc interval has not been studied.

12.3 Pharmacokinetics

The pharmacokinetic parameters of relugolix, unconjugated estradiol, and norethindrone after administration of a single dose of MYFEMBREE to healthy postmenopausal women under fasted conditions are summarized in Table 7.

Table 7: Pharmacokinetic Parameters of Relugolix, Unconjugated Estradiol, and Norethindrone After Single Dose Administration of MYFEMBREE

	Relugolix	Unconjugated Estradiol	Norethindrone
$AUC_{0\text{-}inf}$ (ng·hr/mL or pg·hr/mL), mean (SD)	198.1 (111.6)	818.7 (334.4)	17.5 (8.5)
C_{max} (ng/mL or pg/mL), mean (SD)	26.0 (18.2)	28.0 (19.2)	3.6 (1.4)
T_{max} (hr), median (min, max)	2.00 (0.25, 5.00)	7.00 (0.25, 24.00)	1.0 (0.50, 4.00)

Abbreviations: AUC = area under the concentration-time curve; $AUC_{0\text{-}inf}$ = AUC from time 0 extrapolated to infinity; C_{max} = maximum observed concentration; E2 = estradiol; NET = norethindrone; T_{max} = time to maximum observed concentration.
Notes: $AUC_{0\text{-}inf}$ is presented in ng·hr/mL for relugolix, NET and in pg·hr/mL for unconjugated E2. C_{max} is presented in ng/mL for relugolix, NET and in pg/mL for unconjugated E2.

Relugolix exhibits greater than dose-proportional exposures at doses ranging from 1 mg to 80 mg (0.025 to 2 times the approved recommended dose) and approximately dose-proportional exposures at doses ranging from 80 mg to 360 mg (2 to 9 times the approved recommended dose). Relugolix concentrations reach steady-state within 12 days, and the degree of accumulation is approximately 2-fold, upon once daily administration.

Estradiol and norethindrone concentrations reach steady-state within 2 weeks, with an accumulation of 33% to 47% above concentrations seen after administration of a single dose, upon once daily administration.

Absorption

The mean (%CV) absolute bioavailability of relugolix is 12 (62%).

Effect of Food

The $AUC_{0\text{-}inf}$ and C_{max} of relugolix decreased by 38% and 55%, respectively, after administration of MYFEMBREE following consumption of a high-fat, high-calorie meal (i.e., 800-1000 calorie meal in which 50% of calories are derived from fat) compared with the fasted state; however, the decrease in exposure to relugolix is considered not to be clinically meaningful. No clinically meaningful effects of food on the exposure to estradiol or norethindrone were observed.

Distribution

Plasma protein binding of relugolix is 68% to 71%, primarily to albumin and to a lesser extent to α_1-acid glycoprotein. The mean blood-to-plasma ratio is 0.78. Estradiol circulates in the blood bound to SHBG (36% to 37%) and to albumin (61%), while only approximately 1% to 2% is unbound. Norethindrone also binds to a similar extent to SHBG (36%) and to albumin (61%).

Elimination

After administration of a single dose of MYFEMBREE, the mean (SD) terminal phase elimination half-life ($t_{1/2}$) of relugolix, estradiol, and norethindrone are 61.5 (13.2) hours, 16.6 (7.7) hours, and 10.9 (3.1) hours, respectively.

Metabolism

Relugolix is metabolized primarily by CYP3A and to a lesser extent by CYP2C8 in vitro.

Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is a major urinary metabolite. Estrogens also undergo enterohepatic recirculation due to sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption.

Norethindrone undergoes extensive biotransformation, primarily by reduction, in addition to sulfation, glucuronidation, and oxidation, respectively, by sulfotransferases (SULTs), glucuronosyltransferases (UGTs), and CYP enzymes, including CYP3A4. The majority of metabolites in the circulation are sulfates, with glucuronides accounting for most of the urinary metabolites.

Excretion

After oral administration of a single 80 mg radiolabeled dose of relugolix, approximately 81% of the radioactivity was recovered in feces (4.2% as unchanged) and 4.1% in urine (2.2% as unchanged).

Estradiol is excreted in the urine as glucuronide and sulfate conjugates. Norethindrone is primarily excreted in urine as various polar metabolites.

Specific Populations

No clinically significant differences in the pharmacokinetics of relugolix were observed based on age (19 to 53 years), race/ethnicity (Asian [49%], White [24%], Black/African American [24%]), body

weight (38 to 144 kg), mild to severe renal impairment (creatinine clearance [CLcr] 15 to 89 mL/min, as estimated by the Cockcroft-Gault equation), or mild or moderate hepatic impairment (Child-Pugh A or B). The effects of severe hepatic impairment (Child-Pugh C) or end-stage renal disease with or without hemodialysis on the pharmacokinetics of relugolix have not been studied.

The effects of renal or hepatic impairment on the pharmacokinetics of estradiol or norethindrone have not been studied. However, estradiol blood concentrations are expected to be increased in patients with hepatic impairment compared to patients with normal hepatic function.

Drug Interaction Studies

Clinical Studies

- *Combined P-gp and Moderate CYP3A Inhibitor:* Co-administration with erythromycin (P-gp and moderate CYP3A inhibitor) increased the AUC and C_{max} of relugolix by 6.2-fold.

- *Combined P-gp and Strong CYP3A Inducer:* Co-administration with rifampin (P-gp and strong CYP3A inducer) decreased the AUC and C_{max} of relugolix by 55% and 23%, respectively.

- *Other Drugs:* No clinically significant differences in the pharmacokinetics of relugolix were observed when co-administered with voriconazole (strong CYP3A inhibitor), fluconazole (moderate CYP3A inhibitor), or atorvastatin (weak CYP3A inhibitor). No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A substrate) or rosuvastatin (BCRP substrate) were observed upon co-administration with relugolix.

In Vitro Studies

- *Cytochrome P450 (CYP) Enzymes*: Relugolix is a substrate of CYP3A and CYP2C8. Relugolix is an inducer of CYP3A and CYP2B6, but not an inducer of CYP1A2. Relugolix is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4.

- *Transporter Systems:* Relugolix is a substrate of P-gp, but not a substrate of BCRP. Relugolix is an inhibitor of BCRP and P-gp, but not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Relugolix

Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 142 or 423 times, respectively, the exposure in human females at the MRHD of 40 mg daily, based on AUC.

E2/NETA

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Mutagenesis

Relugolix was not mutagenic in the in vitro bacterial reverse mutation (Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

Impairment of Fertility

In a fertility study in rats, no effect on female fertility was observed at up to 1000 mg/kg/day (300 times the MRHD of 40 mg daily in women). In rats, the binding affinity of relugolix for GnRH receptors is greater than 1000-fold less than in humans, and this study represents an assessment of non-pharmacological targets of relugolix.

In human GnRH-receptor knock-in mice, administration of relugolix at oral doses of 100 mg/kg and above twice daily to female mice induced a constant diestrus phase and decreased ovarian and uterine weights, effects which were reversible following cessation of treatment. In male knock-in mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses 3 mg/kg and above twice daily for 28 days, effects which were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal.

In a 39-week toxicology study in monkeys, a decrease in the frequency of menses was observed in female monkeys at 50 mg/kg/day (99 times the MRHD of 40 mg daily in women, based on AUC), which was partially reversed following a 13-week recovery period. There were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at a dose of 120 mg daily in men, based on AUC).

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, GI tract or testes) after repeated oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis was observed at doses of 100 mg/kg (approximately 30 times the exposure at the MRHD of 40 mg daily in women based on AUC) and above. In a monkey 39-week toxicity study, this effect was observed at doses of 1.5 mg/kg (approximately equal to the MRHD) and above and demonstrated evidence of reversibility after cessation of treatment. The significance of this finding in humans is unknown.

14 CLINICAL STUDIES

14.1 Heavy Menstrual Bleeding Associated with Uterine Fibroids

The efficacy and safety of MYFEMBREE were evaluated in two replicate, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal women with

heavy menstrual bleeding associated with uterine fibroids in Study L1 (NCT03049735) and Study L2 (NCT03103087).

For study inclusion, women had to have uterine fibroids confirmed by ultrasound examination in which at least one fibroid met at least one of the following criteria:

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

Women also had to have menstrual blood loss (MBL) volume of ≥ 80 mL per cycle for two menstrual cycles or ≥ 160 mL during one cycle quantified by the alkaline hematin method from menstrual products collected during baseline menstrual cycles to be included in the studies. Women with hemoglobin < 8.0 g/dL were excluded from the study. Iron therapy was required for women with hemoglobin ≥ 8 g/dL and ≤ 10 g/dL. Women were allowed, but not required, to take calcium and vitamin D during the study.

In Studies L1 and L2, women were randomized 1:1:1 to receive a once daily relugolix 40 mg tablet plus an over encapsulated tablet of E2 1 mg and NETA 0.5 mg (relugolix+E2/NETA), which is equivalent to 1 tablet of MYFEMBREE, for 24 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for 12 weeks followed by MYFEMBREE for 12 weeks. Treatment was initiated within the first seven days after the onset of menses.

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

A total of 768 women were randomized and treated in Studies L1 and L2 (741 women in the efficacy population used for these studies). Of the 741 women, 247 received treatment with MYFEMBREE (122 and 125 in Studies L1 and L2, respectively), 252 received treatment with relugolix followed by MYFEMBREE (125 and 127 in Studies L1 and L2, respectively), and 242 received placebo (113 and 129 in Studies L1 and L2, respectively). The median age of women included in the efficacy analysis was 43 years (19 - 51 years), and mean body mass index was 31.6 kg/m^2. Approximately 53% of study participants were Black, 41% were White, and 6% were of other races. Across studies at baseline, mean (± standard deviation) MBL volume at baseline was 231 mL (± 156). Baseline uterine size in Studies L1 and L2 ranged from normal to greater than 28 weeks gestation size (47 - 2625 cm^3).

Menstrual Blood Loss

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 8).

Table 8: 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, %	55.3%		56.5%	
95% CI	(44.2%, 65.6%)		(46.6%, 66.5%)	
p-value	< 0.0001		< 0.0001	

Abbreviations: CI = confidence interval.

Amenorrhea

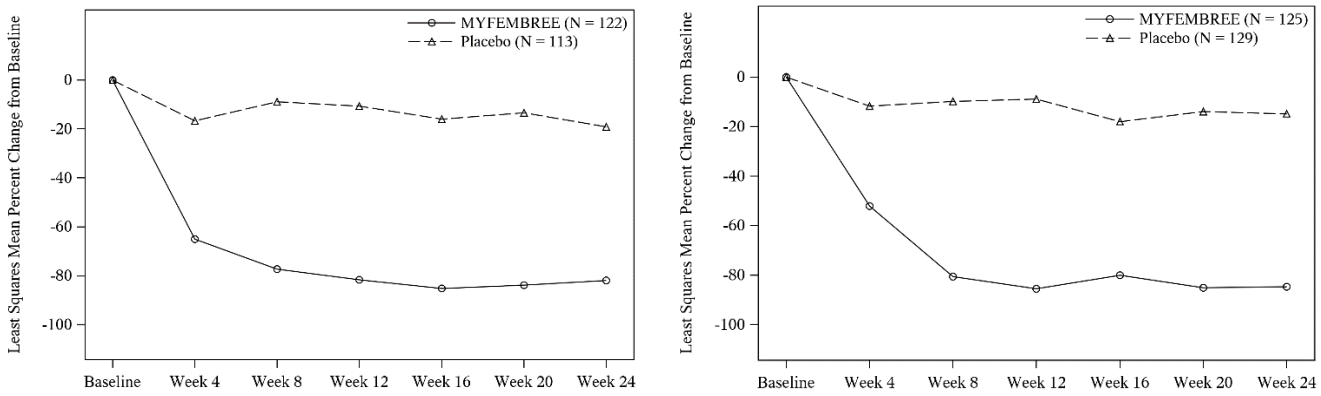
In Studies L1 and L2, 50.0% and 50.4% of women treated with MYFEMBREE, respectively, achieved amenorrhea as compared to 6.2% and 3.1% treated with placebo, respectively, over the last 35 days of treatment.

Percent Change in MBL Volume

The mean MBL volumes in Studies L1 and L2 at baseline were 243.8 mL and 246.7 mL in the MYFEMBREE group and 223.2 mL and 211.8 mL in the placebo group, respectively. The mean reduction in MBL volume from baseline to Week 24 in the MYFEMBREE group was 82.0% in Study L1 and 84.3% in Study L2, which was greater than placebo (19.1% and 15.1%, respectively). Reductions in MBL volume for MYFEMBREE and placebo groups are depicted in Figure 1.

Figure 1: Percent Change from Baseline in Menstrual Blood Loss Over 24 weeks

Study L1 **Study L2**



Hemoglobin Levels

For efficacy, a hemoglobin response was defined as a hemoglobin increase > 2 g/dL from baseline to Week 24 in the subgroup of women with anemia at baseline (hemoglobin ≤ 10.5 g/dL). A statistically higher proportion treated with MYFEMBREE compared with placebo had > 2 g/dL improvement in hemoglobin levels, see Table 9.

Table 9: Proportion of Women with Baseline Hgb ≤ 10.5 and > 2 g/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, %	26.9%		49.3%	
95% CI	(6.7%, 47.2%)		(32.7%, 66.0%)	
p-value	0.0177		<0.0001	

Abbreviation: CI = confidence interval.
n = number of patients with Hgb ≤10.5 g/dL at baseline.
N = number of patients in each treatment group.

Recurrence of Heavy Menstrual Bleeding After Discontinuation of MYFEMBREE

In a randomized withdrawal study (L4), 229 women from the open label extension Study L3 were rerandomized to either continue blinded treatment with MYFEMBREE or withdrawal of therapy (placebo) for an additional 52 weeks. The median time to return to heavy menstrual bleeding among women randomized to placebo (treatment withdrawal) was 5.9 weeks.

14.2 Moderate to Severe Pain Associated with Endometriosis

The efficacy of MYFEMBREE was assessed in two 24-week, multinational, randomized, double-blind, placebo-controlled studies in pre-menopausal women with moderate to severe pain associated with endometriosis in Study S1 (NCT03204318) and Study S2 (NCT03204331).

In Studies S1 and S2, women with moderate to severe pain associated with endometriosis were randomized 1:1:1 to receive once daily treatment with a tablet of relugolix 40 mg plus an over encapsulated tablet of E2 1 mg and NETA 0.5 mg, (equivalent to one tablet of MYFEMBREE) for 24 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for 12 weeks followed by MYFEMBREE for 12 weeks.

For study inclusion, women had to have endometriosis confirmed by direct visualization during surgery and/or histology in addition to pain associated with endometriosis during a placebo run-in period. Dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) were assessed daily using an 11-point numerical rating scale (NRS) ranging from 0 (“no pain”) to 10 (“pain as bad as you can imagine”). Specifically, women had to have pain that met the following criteria:

- DYS NRS score ≥ 4.0 on at least 2 days AND
- Mean NMPP NRS score ≥ 2.5 *or*
  Mean NMPP NRS score ≥ 1.25 and NMPP NRS score ≥ 5.0 on at least 4 days

Studies S1 and S2 each had two co-primary endpoints. The first co-primary endpoint was a responder analysis where a responder was defined as a woman who achieved a reduction from baseline in dysmenorrhea (DYS) NRS of at least 2.8 points over the last 35 days of treatment, without an increase in analgesic use (nonsteroidal anti-inflammatory drug or opioid). The second co-primary endpoint was a responder analysis where a responder was defined as a woman who achieved a reduction from baseline in non-menstrual pelvic pain (NMPP) NRS score of at least 2.1 points over the last 35 days of treatment, without an increase in analgesic use (nonsteroidal anti-inflammatory drug or opioid) for pain associated with endometriosis.

In Study S1, a total of 424 women were included in the efficacy population (212 received MYFEMBREE; 212 received placebo). The median age of the efficacy population was 34 years and the mean body mass index was 26 kg/m^2. Approximately 92% were White, 6% were Black, and 7% were of Hispanic or Latino descent. A total of 19% were from the United States and/or Canada. At baseline, 29% of women used an opioid rescue analgesic for moderate to severe pain associated with endometriosis.

In Study S2, a total of 405 women were included in the efficacy population (205 received MYFEMBREE; 200 received placebo). The median age of the efficacy population was 34 years and the mean body mass index was 26 kg/m^2. Approximately 90% were White, 6% were Black, and 17% were of Hispanic or Latino descent. A total of 24% were from United States and none were from Canada. At baseline, 48% of women used an opioid rescue analgesic for moderate to severe pain associated with endometriosis.

The results for the co-primary efficacy endpoints as assessed at Week 24 are shown below in Table 10.

Table 10: Proportion of Dysmenorrhea and Non-Menstrual Pelvic Pain Responders at Week 24

	Study S1		Study S2	
	MYFEMBREE (N = 212)	**Placebo (N = 212)**	**MYFEMBREE (N = 205)**	**Placebo (N = 200)**
Dysmenorrhea	74.5%	26.9%	75.1%	30.5%
Difference from placebo (95% CI) p-value	47.6% (39.3%, 56.0%) ≤ 0.0001	-	44.6% (35.9%, 53.3%) ≤ 0.0001	-
Non-menstrual pelvic pain	58.5%	39.6%	65.9%	42.5%
Difference from placebo (95% CI) * p-value	18.9% (9.5%, 28.2%) ≤ 0.0001	-	23.4% (13.9%, 32.8%) ≤ 0.0001	-

Abbreviations: CI = confidence interval.
Responders are women with a reduction from baseline of at least 2.8 points on the NRS for dysmenorrhea or at least 2.1 points on the NRS for non-menstrual pelvic pain and no increase in analgesic use over the last 35 days of treatment.

Key secondary efficacy endpoints included changes from baseline in the DYS NRS scores, NMPP NRS scores, Endometriosis Health Profile-30 (EHP-30) pain domain scores, dyspareunia NRS scores, and opioid use.

Reduction in DYS and NMPP NRS Scores

Women treated with MYFEMBREE had a greater reduction in DYS and NMPP NRS scores as compared to placebo from baseline to Week 24 in both Studies S1 and S2 (Figure 2 and Figure 3).

Figure 2: Mean DYS NRS Scores in Study S1 and Study S2 over 24 Weeks

Study S1 **Study S2**

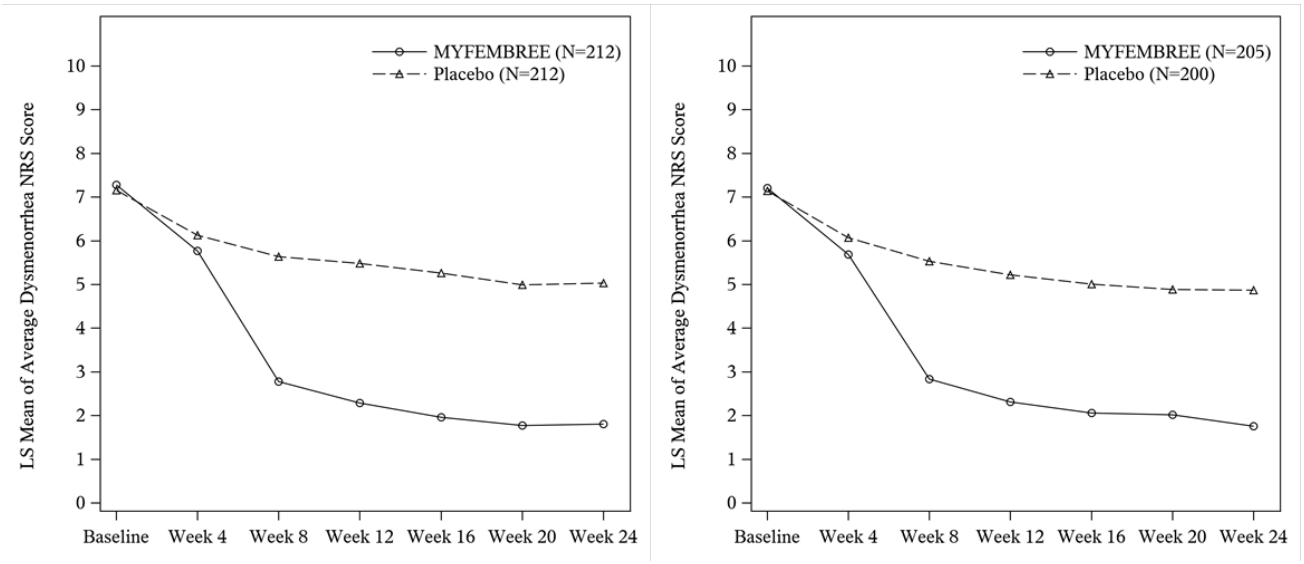
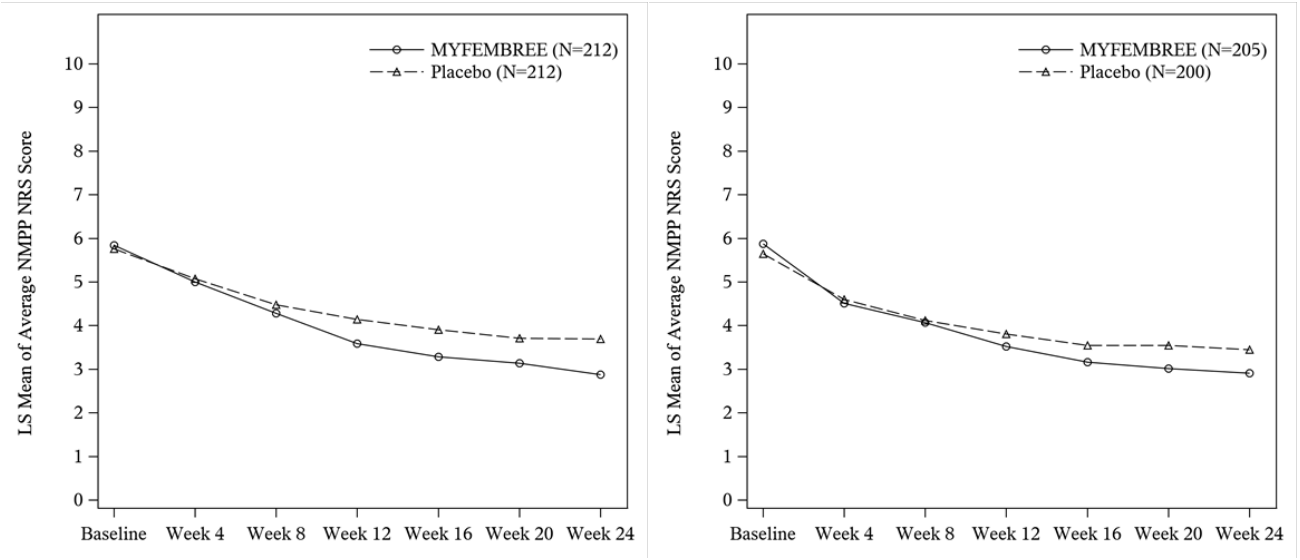


Figure 3: Mean NMPP NRS Scores in Study S1 and Study S2 over 24 Weeks

Study S1 **Study S2**



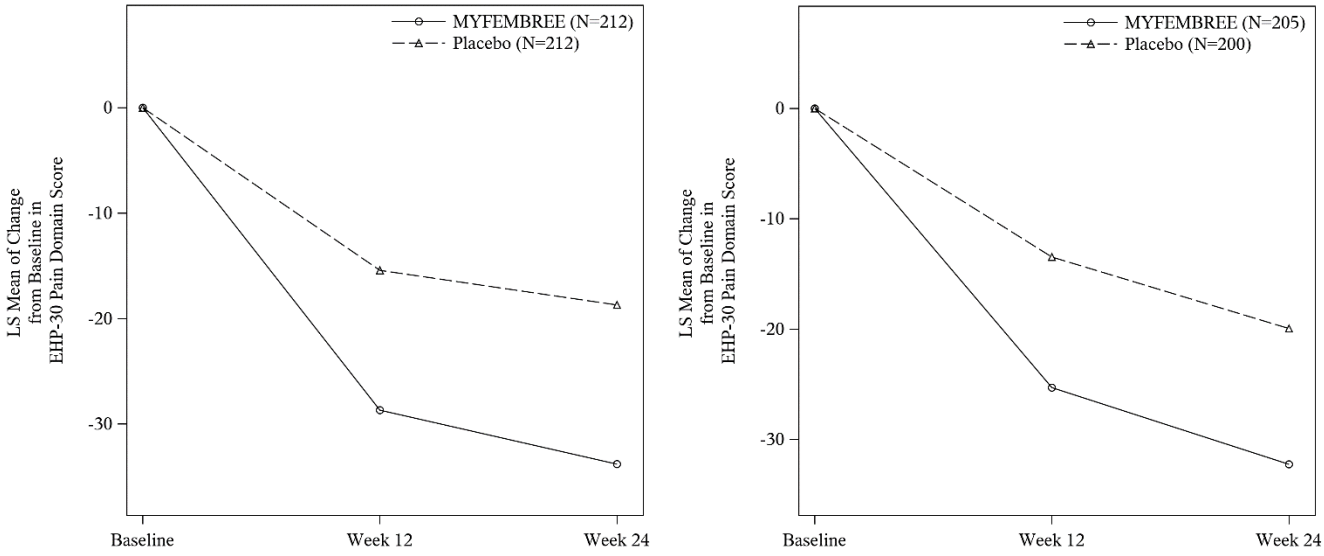
Reduction in EHP-30 Pain Domain Scores

The impact of moderate to severe pain associated with endometriosis was evaluated using the pain domain from the Endometriosis Health Profile-30 (EHP-30), where the domain score (normalized) ranges from 0 to 100 with a higher score representing greater impact of pain on activities.

Women taking MYFEMBREE reported an improvement from baseline in EHP-30 pain domain score compared to placebo at Week 24 in both Studies S1 and S2 (Study S1: -33.8 vs. -18.7 with a treatment difference of -15.1 [95% CI: -19.7, -10.5] and Study S2: -32.2 vs. -20.0 with a treatment difference of -12.3 [95% CI: -16.7, -7.8]). Least squares mean changes in EHP-30 pain domain scores over time are shown in Figure 4.

Figure 4: Mean Change in EHP-30 Pain Domain Scores in Studies S1 and S2 over 24 Weeks

Study S1 **Study S2**



Reduction in Dyspareunia

Dyspareunia associated with endometriosis was evaluated in a subgroup of women who engaged in sexual activity with vaginal intercourse at baseline and during treatment (68% of enrolled women). Dyspareunia (pain during sexual intercourse) was assessed daily using an 11-point NRS ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"). In Studies S1 and S2, women treated with MYFEMBREE had a greater reduction in dyspareunia from baseline to Week 24 compared with placebo [LS mean change in Study S1: -2.4 vs. -1.7, with a treatment difference of -0.7 (95% CI: -1.3, -0.1); in Study S2: -2.4 vs. -1.9, with a treatment difference of -0.5 (95% CI: -1.0, 0.0)].

Use of Opioid Rescue Analgesics

The opioid analgesics used in the studies were tramadol 50 mg, codeine 30 mg, tramadol/acetaminophen (TRM/APAP) 37.5/325 mg, codeine/APAP at strengths of 15/500 mg, 30/300 mg, and 30/500 mg, and hydrocodone/acetaminophen 5/325 mg. The opioid rescue analgesics used at baseline, Month 3, and Month 6 are shown in Table 11.

The clinical relevance of these data has not been demonstrated.

Table 11: Opioid Rescue Analgesic Use in Studies S1 and S2

	Study S1		Study S2	
	MYFEMBREE (N = 212)	**Placebo (N = 212)**	**MYFEMBREE (N = 205)**	**Placebo (N = 200)**
Tablets per month at baseline Mean (SD) Median (Min, Max)	9.1 (12.36) 4.2 (0.6, 60.7)	11.7 (11.95) 7.2 (0.5, 54.6)	9.0 (13.51) 5.6 (0.7, 106.9)	10.0 (12.82) 6.1 (0.4, 86.3)
Tablets per month at Month 3 Mean (SD) Median (Min, Max)	3.9 (7.98) 0.0 (0.0, 32.0)	8.2 (11.48) 3.2 (0.0, 40.8)	3.4 (8.26) 0.0 (0.0, 57.6)	7.5 (23.49) 2.4 (0.0, 215.2)
Tablets per month at Month 6 Mean (SD) Median (Min, Max)	4.8 (10.38) 0.0 (0.0, 45.4)	10.7 (28.93) 3.2 (0.0, 40.8)	2.4 (5.02) 0.0 (0.0, 28.0)	5.6 (14.16) 1.2 (0.0, 120.8)
Number and % of subjects on any dose of opioid rescue at baseline who were off opioid at Month 3*	33/64 (51.6%)	10/56 (17.9%)	46/100 (46.0%)	27/94 (28.7%)
Number and % of subjects on any dose of opioid rescue at baseline who were off opioid at Month 6*	39/64 (60.9%)	18/56 (32.1%)	65/100 (65.0%)	38/94 (40.4%)
Number and % of subjects not on opioid rescue at baseline who were on opioid at Month 3#	4/148 (2.7%)	10/156 (6.4%)	6/105 (5.7%)	15/106 (14.2%)
Number and % of subjects not on any dose of opioid rescue at baseline who were on opioid at Month 6#	5/148 (3.4%)	12/156 (7.7%)	2/105 (1.9%)	12/106 (11.3%)

Max = maximum; Min = minimum; SD = standard deviation; monthly tablets calculations are both on 28-day interval.
* = denominator is the number of subjects on opioid rescue analgesics at baseline.
# = denominator is the number of subjects off opioid rescue analgesics at baseline.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

MYFEMBREE film-coated tablets contain relugolix 40 mg, estradiol (E2) 1 mg, and norethindrone acetate (NETA) 0.5 mg. The tablets are light yellow to yellow, round film-coated tablet with “MVT” on one side and “415” on the other side.

MYFEMBREE is supplied in a white, opaque, high-density polyethylene bottle containing 28 tablets with desiccant and closed with an induction-sealed child-resistant cap (NDC Code 72974-415-01).

16.2 Storage and Handling

Store at 15ºC to 30ºC (59ºF to 86ºF).

Dispose unused medication via a take-back option if available. Otherwise, follow FDA instructions for disposing medication in the household trash, www.fda.gov/drugdisposal. Do NOT flush down the toilet.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Thromboembolic Disorders and Vascular Events

Advise patients that use of estrogen and progestin combinations may increase the risk of venous and arterial thrombotic/thromboembolic events, especially in women at high risk for these events *[see Boxed Warning, Contraindications (4) and Warnings and Precautions (5.1)]*.

Bone Loss

Advise patients about the risk of bone loss. Advise patients that supplementary calcium and vitamin D may be beneficial if dietary intake of calcium and vitamin D is not adequate. Advise women that oral iron supplementation should not be taken at the same time as calcium and vitamin D *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*.

Suicidal Ideation and Mood Disorders (Including Depression)

Advise patients that depression, mood disorders, and suicidal ideation may occur with MYFEMBREE use. Instruct women with new onset or worsening depression, anxiety, or other mood changes to promptly seek medical attention *[see Warnings and Precautions (5.4) and Adverse Reactions (6.1)]*.

Hepatic Impairment and Transaminase Elevations

Advise women to promptly seek medical attention in case of signs or symptoms that may reflect liver injury, such as jaundice *[see Warnings and Precautions (5.5)]*.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

Advise patients that MYFEMBREE may delay the recognition of pregnancy because it may reduce the duration and amount of menstrual bleeding. Advise patients to use effective non-hormonal contraception while taking MYFEMBREE and to discontinue MYFEMBREE if pregnancy is diagnosed *[see Warnings and Precautions (5.8)]*. Advise pregnant patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to MYFEMBREE during pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.

Alopecia

Advise women with uterine fibroids that alopecia, hair loss, and hair thinning in no specific pattern may occur with MYFEMBREE. Advise these women that hair loss and hair thinning may not resolve completely after stopping MYFEMBREE. Advise these women to contact their healthcare provider if they have concerns about changes to their hair *[see Warnings and Precautions (5.11)* and *Adverse Reactions (6.1)]*.

Females of Reproductive Potential

Advise women to use effective non-hormonal contraception while taking MYFEMBREE and for one week after discontinuing treatment and to discontinue MYFEMBREE if pregnancy is confirmed. Advise pregnant patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to MYFEMBREE during pregnancy *[see Use in Specific Populations (8.1, 8.3)]*.

Drug Interactions

Advise women to report their use of any other prescription or nonprescription medications or dietary supplements. Co-administration with certain drugs may decrease the therapeutic effects of MYFEMBREE *[see Drug Interactions (7.1)]*.

Administration Instructions

- Advise women to begin taking MYFEMBREE as soon as possible after the start of menses but no later than 7 days after menses has started *[see Dosage and Administration (2.2)]*.
- Advise women to take any missed dose of MYFEMBREE as soon as possible the same day and then resume regular dosing the next day at the usual time *[see Dosage and Administration (2.3)]*.
- Advise women taking oral P-gp inhibitors to take MYFEMBREE first and separate dosing by at least 6 hours *[see Dosage and Administration (2.4)]*.

Manufactured by Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9, Canada
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214846 MS 005

PATIENT INFORMATION

MYFEMBREE® (mye fem' brē)

(relugolix, estradiol and norethindrone acetate)

tablets, for oral use

What is the most important information I should know about MYFEMBREE?
MYFEMBREE may cause serious side effects, including:

- **cardiovascular conditions**
  - MYFEMBREE may increase your chances of heart attack, stroke, or blood clots, especially if you are over 35 years of age, smoke, and have uncontrolled high blood pressure. **Stop taking MYFEMBREE and call your healthcare provider right away or go to the nearest hospital emergency room right away if you have:**
    - leg pain or swelling that will not go away
    - sudden shortness of breath
    - double vision, bulging of the eyes, or sudden blindness, partial or complete
    - pain or pressure in your chest, arm, or jaw
    - sudden, severe headache unlike your usual headaches
    - weakness or numbness in an arm or leg, or trouble speaking
- **bone loss (decreased bone mineral density)**
  - While you are taking MYFEMBREE, your estrogen levels may be low. Low estrogen levels can lead to bone mineral density loss.
  - If you have bone loss on MYFEMBREE, your bone density may improve after you stop taking MYFEMBREE, but complete recovery may not occur. It is unknown if these bone changes could increase your risk for broken bones as you age. For this reason, **you should not take MYFEMBREE for more than 24 months.**
  - Your healthcare provider may order an X-ray test called a DXA scan to check your bone mineral density when you start taking MYFEMBREE and periodically after you start if you have uterine fibroids or annually if you have pain associated with endometriosis.
  - Your healthcare provider may advise you to take vitamin D and/or calcium supplements as part of a healthy lifestyle that promotes bone health. If you are also advised to take iron supplements, they should be taken at least two hours apart from your vitamin D or calcium supplements.
- **effects on pregnancy**
  - **Do not take** MYFEMBREE if you are trying to become pregnant or are pregnant. It may increase the risk of early pregnancy loss.
  - **If you think you are pregnant**, stop taking MYFEMBREE right away and call your healthcare provider.
    - If you become pregnant while taking MYFEMBREE, you are encouraged to enroll in the Pregnancy Registry. The purpose of the pregnancy registry is to collect information about the health of you and your baby. Talk to your healthcare provider or call 1-(855) 428-0707.
  - MYFEMBREE can decrease your menstrual bleeding or result in no menstrual bleeding at all, making it hard to know if you are pregnant. Watch for other signs of pregnancy such as breast tenderness, weight gain and nausea.
  - MYFEMBREE does not prevent pregnancy. You will need to use effective methods of birth control while taking MYFEMBREE and for 1 week after you stop taking MYFEMBREE. Examples of effective methods can include condoms or spermicide, which do not contain hormones.
  - Do not take hormonal birth control such as birth control pills because they may increase your side effects and MYFEMBREE may not work as well.

    Talk to your healthcare provider about which birth control to use during treatment with MYFEMBREE. Your healthcare provider may change the birth control you were on before you start taking MYFEMBREE.

What is MYFEMBREE?

- MYFEMBREE is a prescription medicine used in premenopausal women (before “change of life” or menopause) to

- control heavy menstrual bleeding due to uterine fibroids or
- manage moderate to severe pain associated with endometriosis.

- MYFEMBREE contains relugolix, which reduces the amount of estrogen (and other hormones) produced by ovaries, estradiol (an estrogen) which may reduce the risk of bone loss, and norethindrone acetate (a progestin) which is necessary when women with a uterus (womb) take estrogen.
- It is not known if MYFEMBREE is safe to use more than 24 months due to the risk of continued bone loss that may not be reversible.
- It is not known if MYFEMBREE is safe and effective in children under 18 years of age.

Do not take MYFEMBREE if you:

- have or have had:
  - blood clots in your legs (deep vein thrombosis), lungs (pulmonary embolism), or eyes (retinal thrombosis)
  - stroke or heart attack
  - a problem that makes your blood clot more than normal
  - blood circulation disorders
  - certain heart valve problems or heart rhythm abnormalities that can cause blood clots to form in the heart
  - high blood pressure not well controlled by medicine
  - diabetes with kidney, eye, nerve, or blood vessel damage
  - certain kinds of severe migraine headaches with aura, numbness, weakness or changes in vision or migraine headaches if you are over age 35
  - breast cancer or any cancer that is sensitive to female hormones
  - osteoporosis
  - vaginal bleeding that has not been diagnosed. Your healthcare provider should check any unexplained vaginal bleeding to find out the cause.
  - liver problems including liver disease
- smoke and are over 35 years old
- have had a serious allergic reaction with symptoms that included swelling of your face, lips, mouth or tongue, trouble breathing, skin rashes, redness, or swelling or an allergic reaction to relugolix, estradiol, norethindrone or any of the ingredients in MYFEMBREE. See the end of this Patient Package Insert for a complete list of ingredients in MYFEMBREE.

Before you take MYFEMBREE, tell your healthcare provider about all of your medical conditions including if you:

- have or have had:
  - broken bones or other conditions that may cause bone problems.
  - depression, mood swings, or suicidal thoughts or behavior.
  - yellowing of the skin or eyes (jaundice) or jaundice caused by pregnancy (cholestasis of pregnancy).
- are scheduled for surgery or will be on bed rest. MYFEMBREE may increase your risk of blood clots after surgery. Your healthcare provider may advise you to stop taking MYFEMBREE before you have surgery. Talk to your healthcare provider about when to stop MYFEMBREE before surgery and when to restart MYFEMBREE after surgery.
- are pregnant or think you may be pregnant or just had a baby.
- are breastfeeding. MYFEMBREE may pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take MYFEMBREE.

Tell your healthcare provider about all the medicines you take, including prescription, over-the-counter medicines, vitamins, and herbal supplements.
Women on thyroid or cortisol replacement therapy may need increased doses of the hormone.
Know the medicines you take. Keep a list of your medicines with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take MYFEMBREE?

- Take MYFEMBREE exactly as your healthcare provider tells you to take it.
- Take MYFEMBREE 1 time each day at about the same time with or without food.
- If you have to take oral P-gp inhibitors, take MYFEMBREE first and wait at least 6 hours before taking the P-gp inhibitor. Ask your healthcare provider if you are not sure if you are taking this type of medicine.
- Your healthcare provider may give you a pregnancy test before you start taking MYFEMBREE.
- You should begin MYFEMBREE as soon as possible after your period begins, but no later than 7 days after your period has started. If you start MYFEMBREE on another day, your period may become heavy or irregular for the first month after starting treatment, but bleeding should decrease after this time.
- If you take too much MYFEMBREE, call your healthcare provider or go to the nearest hospital emergency room right away.
- **If you miss a dose**, take the missed dose as soon as you remember on that day, and then take MYFEMBREE at the usual time the next day.
- **Do not take** 2 doses at once to make up for the missed dose. If you do not remember until you are due for MYFEMBREE on the next day, do not make up for the missed dose.

What are the possible side effects of MYFEMBREE?
MYFEMBREE may cause serious side effects including:

- **See "What is the most important information I should know about MYFEMBREE?"**
- **suicidal thoughts, suicidal behavior, and worsening of mood. Call your healthcare provider or get emergency medical help right away if you have any of these symptoms, especially if they are new, worse, or bother you:**
  - thoughts about suicide or dying
  - attempts to commit suicide
  - new or worse depression
  - new or worse anxiety
  - other unusual changes in behavior or mood

  Pay attention to any changes, especially sudden changes in your mood, behaviors, thoughts, or feelings.
- **abnormal liver tests. Call your healthcare provider right away if you have any of these signs and symptoms of liver problems:**
  - jaundice
  - dark, amber-colored urine
  - feeling tired (fatigue or exhaustion)
  - nausea and vomiting
  - generalized swelling
  - right upper stomach area (abdomen) pain
  - bruising easily
- **gallbladder problems** (cholestasis), especially if you had cholestasis of pregnancy.
- **high blood pressure.** See your healthcare provider to check your blood pressure regularly.
- **uterine fibroid prolapse or expulsion.** Fibroids can come out completely or partially through the vagina. Call your healthcare provider right away if you have increased bleeding from the vagina, which can be serious, or cramping, while taking MYFEMBREE.
- **hair loss (alopecia).** In women with uterine fibroids, hair loss and hair thinning can happen while taking MYFEMBREE. It is not known if this hair loss or hair thinning stops after you stop taking MYFEMBREE or is reversible. Talk to your healthcare provider if this is a concern for you.
- **increases in the blood sugar, cholesterol and fat (triglycerides) levels in your blood.**
- **changes in laboratory tests** including thyroid, steroid, hormone, cholesterol, and blood clotting tests.

The most common side effects of MYFEMBREE in women that have heavy bleeding with uterine fibroids include:

- hot flushes
- increased sweating
- night sweats

- abnormal vaginal bleeding (bleeding that lasts too long, that is too much, or is unexpected)
- hair loss or hair thinning
- decreased interest in sex

The most common side effects of MYFEMBREE in women that have moderate to severe pain with endometriosis include:

- headache
- hot flushes, sweating, or night sweats
- mood changes including worsening depression
- abnormal vaginal bleeding (bleeding that lasts too long, that is too much, or is unexpected)
- nausea
- toothache
- back pain
- decreased interest in sex
- joint pain
- tiredness
- dizziness

These are not all the possible side effects of MYFEMBREE. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store MYFEMBREE?

- Store MYFEMBREE between 59°F to 86°F (15°C to 30°C).
- Dispose of unused medicines through community take-back disposal programs when available. If no community take-back disposal program is available go to www.fda.gov/drugdisposal for information on how to dispose of MYFEMBREE the right way.
- **Do not** flush MYFEMBREE down the toilet.
- Do not keep medicine that is out of date or that you no longer need.
- **Keep MYFEMBREE and all medicines out of the reach of children.**

General information about the safe and effective use of MYFEMBREE.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use MYFEMBREE for a condition for which it was not prescribed. Do not give MYFEMBREE to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about MYFEMBREE that is written for health professionals.

What are the ingredients of MYFEMBREE?

Active ingredient: relugolix, estradiol, and norethindrone acetate

Inactive ingredients: lactose monohydrate, mannitol, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hypromellose, titanium dioxide, triacetin, iron oxide yellow.

Manufactured by: Patheon Inc., Mississauga, Ontario, Canada

Manufactured for: Sumitomo Pharma America, Marlborough, MA 01752

For more information, call Sumitomo Pharma America at 1-833-696-8268 or go to www.MYFEMBREE.com

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