

## 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  $\geq$  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  $\geq$  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](http://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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1 **FULL PRESCRIBING INFORMATION**  
2

**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)].**

3  
4 **1 INDICATIONS AND USAGE**  
5

6 **1.1 Heavy Menstrual Bleeding Associated with Uterine Leiomyomas**

7 MYFEMBREE is indicated for the management of heavy menstrual bleeding associated with  
8 uterine leiomyomas (fibroids) in premenopausal women [see Clinical Studies (14)].  
9

10 **1.2 Moderate to Severe Pain Associated with Endometriosis**

11 MYFEMBREE is indicated for the management of moderate to severe pain associated with  
12 endometriosis in premenopausal women [see Clinical Studies (14)].  
13

14 **1.3 Limitations of Use**

15 Use of MYFEMBREE should be limited to 24 months due to the risk of continued bone loss that  
16 may not be reversible [see Warnings and Precautions (5.2) and Adverse Reactions (6)].  
17

18 **2 DOSAGE AND ADMINISTRATION**  
19

20 **2.1 Prior to Initiation of MYFEMBREE**  
21

- Exclude pregnancy [see Contraindications (4)].
  - Discontinue hormonal contraceptives [see Warnings and Precautions (5.8)].
- 24

25 **2.2 Recommended Dosage**  
26

- 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)].
- 30

- 31 • The recommended total duration of treatment with MYFEMBREE is 24 months [see  
32 *Indications and Usage (1.3), Warnings and Precautions (5.2), and Adverse Reactions (6)*].  
33

### 34 **2.3 Missed Dose**

35  
36 Take the missed dose of MYFEMBREE as soon as possible the same day and then resume regular  
37 dosing the next day at the usual time.  
38

### 39 **2.4 Dosage Modification for Concomitant Use with P-gp Inhibitors**

40  
41 Avoid concomitant use of MYFEMBREE with oral P-gp inhibitors. If concomitant use is  
42 unavoidable, take MYFEMBREE first and separate dosing by at least 6 hours [see *Drug Interactions*  
43 *(7.1) and Clinical Pharmacology (12.3)*].  
44

## 45 **3 DOSAGE FORMS AND STRENGTHS**

46  
47 Tablets: Each tablet of MYFEMBREE contains a fixed-dose combination of relugolix 40 mg, estradiol  
48 (E2) 1 mg, and norethindrone acetate (NETA) 0.5 mg. The tablets are light yellow to yellow, round,  
49 film-coated, and debossed with “MVT” on one side and “415” on the other side.  
50

## 51 **4 CONTRAINDICATIONS**

52  
53 MYFEMBREE is contraindicated in women:

- 54 • With a high risk of arterial, venous thrombotic, or thromboembolic disorders [see *Boxed Warning*  
55 *and Warnings and Precautions (5.1)*]. Examples include women over 35 years of age who smoke  
56 and women who are known to have:
- 57 ◦ current or history of deep vein thrombosis or pulmonary embolism
  - 58 ◦ vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular  
59 disease)
  - 60 ◦ thrombotic valvular or thrombotic rhythm diseases of the heart (e.g., subacute bacterial  
61 endocarditis with valvular disease, or atrial fibrillation)
  - 62 ◦ inherited or acquired hypercoagulopathies
  - 63 ◦ uncontrolled hypertension
  - 64 ◦ headaches with focal neurological symptoms or migraine headaches with aura if over 35 years of  
65 age
- 66 • Who are pregnant. Exposure to MYFEMBREE early in pregnancy may increase the risk of early  
67 pregnancy loss [see *Warnings and Precautions (5.9) and Use in Specific Populations (8.1)*].
- 68 • With known osteoporosis, because of the risk of further bone loss [see *Warnings and Precautions*  
69 *(5.2)*].
- 70 • With current or history of breast cancer or other hormone-sensitive malignancies, and with increased  
71 risk for hormone-sensitive malignancies [see *Warnings and Precautions (5.3)*].
- 72 • With known hepatic impairment or disease [see *Warnings and Precautions (5.5)*].
- 73 • With undiagnosed abnormal uterine bleeding.
- 74 • With known anaphylactic reaction, angioedema, or hypersensitivity to MYFEMBREE or any of its  
75 components. Anaphylactoid reactions, urticaria, and angioedema have been reported [see *Warnings*  
76 *and Precautions (5.14), Adverse Reactions (6.2)*].

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## 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.

122 **5.3 Hormone-Sensitive Malignancies**

123  
124 MYFEMBREE is contraindicated in women with current or a history of hormone-sensitive malignancies  
125 (e.g., breast cancer) and in women at increased risk for hormone-sensitive malignancies [see  
126 *Contraindications (4)*]. Discontinue MYFEMBREE if a hormone-sensitive malignancy is diagnosed.

127  
128 Surveillance measures in accordance with standard of care, such as breast examinations and  
129 mammography, are recommended. The use of estrogen alone or estrogen plus progestin has been  
130 reported to result in an increase in abnormal mammograms requiring further evaluation.

131  
132 **5.4 Suicidal Ideation and Mood Disorders (Including Depression)**

133  
134 Evaluate patients with a history of suicidal ideation, depression, and mood disorders prior to initiating  
135 treatment. Monitor patients for mood changes and depressive symptoms including shortly after  
136 initiating treatment, to determine whether the risks of continuing therapy with MYFEMBREE outweigh  
137 the benefits. Patients with new or worsening depression, anxiety, or other mood changes should be  
138 referred to a mental health professional, as appropriate. Advise patients to seek immediate medical  
139 attention for suicidal ideation and behavior. Re-evaluate the benefits and risks of continuing  
140 MYFEMBREE if such events occur.

141  
142 Gonadotropin-releasing hormone receptor antagonists, including MYFEMBREE, have been associated  
143 with mood disorders (including depression) and suicidal ideation.

144  
145 In Studies L1 and L2 in women with heavy menstrual bleeding associated with uterine fibroids, a greater  
146 proportion of women treated with MYFEMBREE compared with placebo reported depression  
147 (including depression, mood swings, and depressed mood) (2.4% vs. 0.8%), irritability (2.4% vs. 0%),  
148 and anxiety (1.2% vs. 0.8%) [see *Adverse Reactions (6.1)*].

149  
150 In Studies S1 and S2 in women with moderate to severe pain associated with endometriosis, a greater  
151 proportion of women treated with MYFEMBREE as compared to placebo reported mood disorders  
152 (including depression) (9.1% vs. 7.2%). In addition, cases of suicidal ideation were reported with  
153 MYFEMBREE use. All women who reported suicidal ideation had a history of depression and/or  
154 anxiety [see *Adverse Reactions (6.1)*].

155  
156 **5.5 Hepatic Impairment and Transaminase Elevations**

157  
158 Contraindication in Patients with Hepatic Impairment

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

162  
163 Transaminase Elevations

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

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

168

169 In placebo-controlled clinical trials, in women with uterine fibroids or endometriosis, elevations ( $\geq 3$   
170 times the upper limit of the normal [ULN] of reference range) in alanine aminotransferase (ALT)  
171 occurred in 0.4% (1/254) and 0.7% (3/418) of MYFEMBREE-treated women, respectively, as compared  
172 to 0% (0/256) and 0.5% (2/416) of placebo-treated women, respectively; moreover, elevations ( $\geq 3$   
173 times ULN of reference range) in aspartate aminotransferase (AST) occurred in 0.8% (2/254) and 0.2%  
174 (1/418) of MYFEMBREE-treated women, respectively, as compared to 0.4% (1/256) and 0.5% (2/416)  
175 of placebo-treated women, respectively. No patterns in time to onset of these liver transaminase  
176 elevations were identified.

177

## 178 **5.6 Gallbladder Disease or History of Cholestatic Jaundice**

179

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

184

## 185 **5.7 Elevated Blood Pressure**

186

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

190

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

195

## 196 **5.8 Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy**

197

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

205

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

211

212 **5.9 Risk of Early Pregnancy Loss**

213  
214 MYFEMBREE is contraindicated for use in pregnancy [see *Contraindications (4)*]. Based on findings  
215 from animal studies and its mechanism of action, MYFEMBREE can cause early pregnancy loss.  
216 However, in both rabbits and rats, no fetal malformations were present at any dose level tested which  
217 were associated with relugolix exposures about half and approximately 300 times exposures in women  
218 at the recommended human dose [see *Use in Specific Populations (8.1)*].

219  
220 **5.10 Uterine Fibroid Prolapse or Expulsion**

221  
222 Advise women with known or suspected submucosal uterine fibroids about the possibility of uterine  
223 fibroid prolapse or expulsion and instruct them to contact their physician if severe bleeding and/or  
224 cramping occurs while being treated with MYFEMBREE. In Studies L1 and L2, uterine fibroid prolapse  
225 or uterine fibroid expulsion were reported in women treated with MYFEMBREE [see *Adverse*  
226 *Reactions (6.1)*].

227  
228 **5.11 Alopecia**

229  
230 Consider discontinuing MYFEMBREE if hair loss becomes a concern [see *Adverse Reactions (6.1)*].

231  
232 In Phase 3 placebo-controlled clinical trials in women with heavy menstrual bleeding associated with  
233 uterine fibroids, 3.5% of MYFEMBREE-treated women experienced alopecia, hair loss, and hair  
234 thinning as compared to 0.8% of placebo-treated women. In 3 of the 11 affected women treated with  
235 MYFEMBREE across Studies L1 and L2, alopecia was reported as moderate. For one MYFEMBREE-  
236 treated woman in the extension trial, alopecia was a reason for discontinuing treatment. No specific  
237 pattern of hair loss was described. The majority of affected women completed the study with reported  
238 hair loss ongoing. Whether the hair loss is reversible is unknown [see *Adverse Reactions (6.1)*].

239  
240 **5.12 Effects on Carbohydrate and Lipid Metabolism**

241  
242 More frequent monitoring in MYFEMBREE-treated women with prediabetes and diabetes may be  
243 necessary. MYFEMBREE may decrease glucose tolerance and result in increased blood glucose  
244 concentrations.

245  
246 Monitor lipid levels and consider discontinuing MYFEMBREE if hypercholesterolemia or  
247 hypertriglyceridemia worsens. In women with pre-existing hypertriglyceridemia, estrogen therapy may  
248 be associated with elevations in triglycerides levels leading to pancreatitis. Use of MYFEMBREE is  
249 associated with increases in total cholesterol and low-density lipoprotein cholesterol (LDL-C) [see  
250 *Adverse Reactions (6.1)*].

251  
252 **5.13 Effect on Other Laboratory Results**

253  
254 Patients with hypothyroidism and hypoadrenalism may require higher doses of thyroid hormone or  
255 cortisol replacement therapy.

256



257 The use of estrogen and progestin combinations may raise serum concentrations of binding proteins  
258 (e.g., thyroid-binding globulin, corticosteroid-binding globulin), which may reduce free thyroid or  
259 corticosteroid hormone levels.

260  
261 The use of estrogen and progestin may also affect the levels of sex hormone-binding globulin, and  
262 coagulation factors [see *Clinical Pharmacology (12.2)*].

263

## 264 **5.14 Hypersensitivity Reactions**

265

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

271

## 272 **6 ADVERSE REACTIONS**

273

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

- 275 • Thromboembolic Disorders and Vascular Events [see *Warnings and Precautions (5.1)*]
- 276 • Bone Loss [see *Warnings and Precautions (5.2)*]
- 277 • Suicidal Ideation and Mood Disorders (Including Depression) [see *Warnings and Precautions*  
278 *(5.4)*]
- 279 • Hepatic Impairment and Transaminase Elevations [see *Warnings and Precautions (5.5)*]
- 280 • Elevated Blood Pressure [see *Warnings and Precautions (5.7)*]
- 281 • Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy [see  
282 *Warnings and Precautions (5.8)*]
- 283 • Uterine Fibroid Prolapse or Expulsion [see *Warnings and Precautions (5.10)*]
- 284 • Alopecia [see *Warnings and Precautions (5.11)*]
- 285 • Effects on Carbohydrate and Lipid Metabolism [see *Warnings and Precautions (5.12)*]
- 286 • Hypersensitivity Reactions [see *Warnings and Precautions (5.14)*]

287

### 288 **6.1 Clinical Trials Experience**

289

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

293

#### 294 Heavy Menstrual Bleeding Associated with Uterine Leiomyomas

295

296 The safety of MYFEMBREE was evaluated in two placebo-controlled clinical trials, Study L1  
297 (LIBERTY 1) and Study L2 (LIBERTY 2), in women with heavy menstrual bleeding associated with  
298 uterine fibroids. In these trials, women received a once daily relugolix 40-mg tablet and an over-  
299 encapsulated tablet of E2 1 mg and NETA 0.5 mg (relugolix + E2/NETA), which is equivalent to 1  
300 tablet of MYFEMBREE. Across the two trials, 254 women received MYFEMBREE once daily for  
301 24 weeks. Additionally, 256 women received placebo for 24 weeks, and 258 women received relugolix  
302 40-mg monotherapy once daily for 12 weeks followed by MYFEMBREE for 12 weeks [see *Clinical*

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

309  
 310 *Serious Adverse Reactions*

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

315  
 316 *Adverse Reactions Leading to Study Drug Discontinuation*

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

321  
 322 *Common Adverse Reactions*

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

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

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

329 <sup>1</sup> Includes hot flush, hyperhidrosis, or night sweats.

330 <sup>2</sup> Includes menorrhagia, metrorrhagia, vaginal hemorrhage, polymenorrhea, and menstruation irregular.

331 <sup>3</sup> Includes libido decreased and loss of libido.

332

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

335

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

338  
339 *Less Common Adverse Reactions*

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

345  
346 *Bone Loss*

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

349 **Table 2: Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in**  
350 **Women with Heavy Menstrual Bleeding Associated with Uterine Fibroids in Studies**  
351 **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	

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

353  
354 In the open-label extension trial, Study L3, women received an additional 28 weeks of MYFEMBREE  
355 for a total of up to 52 weeks of treatment. Women from Study L3 showed continued bone loss at  
356 Months 6 and 12 when treated with up to 52 weeks of MYFEMBREE. The least squares mean percent  
357 changes from baseline in lumbar spine BMD at Months 6 and 12 are presented below in [Table 3](#).

358 **Table 3: Mean Percent Change (On-Treatment) from Baseline\* in Lumbar Spine BMD at**  
359 **Month 6\* and Month 12 for MYFEMBREE-Treated Women with Heavy Menstrual**  
360 **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)

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

362 \* Baseline and Month 6 assessments include only those participants from Studies L1 and L2 who participated in Study L3.

363

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

371  
372 A decline in lumbar spine BMD of > 3% was observed in 23% (30/132) of women who had a DXA scan  
373 following 12 months of MYFEMBREE treatment in Study L3 and in 17.4% (37/213) of untreated  
374 women in the Observational Uterine Fibroids Cohort. A decline of > 8% was seen in 0.8% (1/132) of  
375 women treated with MYFEMBREE who completed a DXA scan at Month 12 and in 0.9% (2/213) of  
376 untreated women in the Observational Uterine Fibroids Cohort.

377  
378 In Studies L1, L2, and L3, four of women treated with MYFEMBREE experienced low trauma fractures  
379 (defined as a fall from standing height or less). Two women, one from Study L1 and one from Study L2,  
380 fractured after 117 and 166 days of treatment with MYFEMBREE. Two women in Study L3, both  
381 treated with relugolix monotherapy for 12 weeks prior to MYFEMBREE therapy, fractured after 149  
382 and 164 days of treatment with MYFEMBREE.

383  
384 *Depression, Mood Disorders, and Suicidal Ideation*

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

389  
390 *Resumption of Menstruation after Discontinuation*

391 Post study menstrual status was available for 35 women in Study L1 and 30 women in Study L2 who  
392 were treated with MYFEMBREE and prematurely discontinued the study or did not continue into the  
393 long-term extension study. For these women, 100% (35/35) in Study L1 and 93.3% (28/30) in Study L2  
394 resumed menses. The mean time from last dose to occurrence of menses was 36 days in Study L1 and  
395 30.7 days in Study L2. Mean time to occurrence of menses was longer for women who achieved  
396 amenorrhea (40.6 days and 41.1 days in Studies L1 and L2, respectively) compared with women without  
397 amenorrhea (33.0 days and 26.6 days in Studies L1 and L2, respectively) in the last 35 days of  
398 treatment. After 12 months of treatment with MYFEMBREE (Study L1 or Study L2, then Study L3)  
399 93.8% (61/65) of women resumed menses. Mean time from last dose of drug to occurrence of menses  
400 was 40.5 days. Mean time to occurrence of menses was longer in women who reported amenorrhea over  
401 the last 35 days of treatment compared with women without amenorrhea over the last 35 days of  
402 treatment (45.6 days vs. 32.6 days, respectively).

403  
404 Women who did not have a return to menses included those who had surgery, used alternative  
405 medications associated with amenorrhea, entered menopause, and unknown cause.

406

407 *Increases in Lipids*

408 Lipid levels were assessed at baseline and Week 24/End of Treatment in Studies L1 and L2. Among  
409 women with normal total cholesterol (< 200 mg/dL) at baseline, increases to 200 to < 240 mg/dL were  
410 seen in 13.7% of women treated with MYFEMBREE as compared to 7.7% of women treated with  
411 placebo, and increases to  $\geq$  240 mg/dL were seen in 1.7% and 0.6% of MYFEMBREE- and placebo-  
412 treated women, respectively. For women with LDL < 130 mg/dL at baseline, increases to 130 to  
413 < 160 mg/dL, 160 to < 190 mg/dL and  $\geq$  190 mg/dL were seen in 9.3%, 1.5%, and 0.5% of women  
414 treated with MYFEMBREE as compared to 6.5%, 0.5% and 0% of women treated with placebo,  
415 respectively.

416

417 Moderate to Severe Pain Associated with Endometriosis

418

419 The safety of MYFEMBREE was evaluated in two placebo-controlled clinical trials, Study S1 and  
420 Study S2, in women with moderate to severe pain associated with endometriosis. In these trials, women  
421 received once daily one relugolix 40-mg tablet with one over-encapsulated tablet of E2 1 mg and NETA  
422 0.5 mg (relugolix + E2/NETA), which is equivalent to one tablet of MYFEMBREE. Across the two  
423 trials, 418 women received MYFEMBREE once daily for 24 weeks, 416 women received placebo for 24  
424 weeks, and 417 women received relugolix 40 mg monotherapy once daily for 12 weeks followed by  
425 MYFEMBREE for 12 weeks [see *Clinical Studies (14)*]. Of these, 799 women were treated with  
426 MYFEMBREE in an 80-week extension trial, Study S3, for a total treatment duration of up to 24  
427 months. Demographics were similar across these trials; 91% were white, 6% were Black, and 12% were  
428 of Hispanic or Latino ethnicity. The mean age at study entry was 34 years (range 18 to 50 years).

429

430 *Serious Adverse Reactions*

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

434

435 *Adverse Reactions Leading to Study Drug Discontinuation*

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

440

441 *Common Adverse Reactions*

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

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

<b>Adverse Reaction</b>	<b>MYFEMBREE (N = 418) %</b>	<b>Placebo (N = 416) %</b>
Headache	33.0	26.4
Vasomotor symptoms <sup>1</sup>	13.2	7.2
Mood disorders <sup>2</sup>	9.1	7.2
Abnormal uterine bleeding <sup>3</sup>	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 <sup>4</sup>	4.3	1.2
Arthralgia	3.6	2.2
Fatigue	3.1	2.4
Dizziness	3.1	1.2

447

448 <sup>1</sup> Includes hot flush, hyperhidrosis, night sweats, and flushing.

449 <sup>2</sup> Includes affect lability, affective disorder, anxiety, depressed mood, depression, emotional distress, generalized anxiety  
450 disorder, irritability, mixed anxiety and depressive disorder, mood altered, mood swings, and suicidal ideation.

451 <sup>3</sup> Includes menorrhagia, metrorrhagia, vaginal hemorrhage, uterine hemorrhage, polymenorrhea, and menstruation irregular.

452 <sup>4</sup> Includes libido decreased, libido disorder, and female sexual arousal disorder.

453

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

456

457 *Less Common Adverse Reactions*

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

461

462

463

464 *Bone Loss*

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

468 **Table 5: LS Mean Percent Change (On-Treatment) from Baseline in Lumbar Spine BMD in**  
 469 **Women with Moderate to Severe Pain Associated with Endometriosis at Month 6 in**  
 470 **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	

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

472

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

478 **Table 6: LS Mean Percent Change (On-Treatment) from Baseline\* in Lumbar Spine BMD at**  
 479 **Months 6\*, 12, and 24 for Women with Moderate to Severe Pain Associated with**  
 480 **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)

481 Abbreviations: LS = least squares; BMD = bone mineral density; CI = confidence interval; N = number of subjects who received  
 482 continuous MYFEMBREE treatment throughout Studies S1/S2 and S3; n = number of subjects who had BMD assessments.

483 \* Baseline and Month 6 assessments include only those participants from Studies S1 and S2 who also participated in Study S3.

484

485

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

488 A separate concurrent prospective observational study enrolled 452 women with moderate to severe pain  
489 associated with endometriosis who were age-matched to participants of Studies S1 and S2. While these  
490 women were not randomized to receive treatment for moderate to severe pain associated with  
491 endometriosis, women were permitted to receive treatment from their provider for this indication.  
492 Women underwent DXA scans at baseline and Months 6 and 12 to monitor for changes in BMD. The  
493 mean percent changes from baseline (95% CI) in lumbar spine BMD at Months 6 and 12 were 0.35  
494 (0.13, 0.57) and 0.53 (0.24, 0.83), respectively.

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

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

507 BMD loss may not be completely reversible after stopping treatment.

508

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

514

#### 515 *Suicidal Ideation and Mood Disorders (Including Depression)*

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

518

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

520

#### 521 *Resumption of Menstruation after Discontinuation*

522 Post-study menstrual status was available for 55 women in Study S1 and 59 women in Study S2 who  
523 were treated with MYFEMBREE and either prematurely discontinued the study or did not continue into  
524 the extension study. For these women, 83.6% (46/55) in Study S1 and 84.7% (50/59) in Study S2  
525 resumed menses. The mean time from last dose to occurrence of menses was 27.1 days in Study S1 and  
526 39.2 days in Study S2. Mean time to occurrence of menses was longer for women who achieved  
527 amenorrhea (34.3 days and 42.8 days in Studies S1 and S2, respectively) compared with women without  
528 amenorrhea (21.0 days and 32.1 days in Studies S1 and S2, respectively) in the last 28 days of treatment.  
529 After 12 months of treatment with MYFEMBREE (Study S1 or Study S2, then Study S3), 97.9%



530 (46/47) of women resumed menses. Mean time from last dose of drug to occurrence of menses was 36.7  
531 days.

532

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

535

### 536 *Increases in Lipids*

537 Lipid levels were assessed at baseline and Week 24/End of Treatment in Studies S1 and S2. Among  
538 women with normal total cholesterol (< 200 mg/dL) at baseline, increases to  $\geq 200$  to < 240 mg/dL were  
539 seen in 13.6% (41/302) of MYFEMBREE- treated women as compared to 9.3% (27/289) of placebo-  
540 treated women, and increases to  $\geq 240$  mg/dL were seen in 0.7% (2/302) of MYFEMBREE-treated  
541 women as compared to 1.0% (3/289) of placebo-treated women. For women with LDL < 130 mg/dL at  
542 baseline, increases to 130 to < 160 mg/dL, 160 to < 190 mg/dL and  $\geq 190$  mg/dL were seen in 8.0%,  
543 0.3%, and 0% of MYFEMBREE-treated women as compared to 7.6%, 0% and 0% of placebo-treated  
544 women. Among women with normal HDL at baseline ( $\geq 60$  mg/dL), declines to 40 to < 60 mg/dL  
545 occurred in 22.2% (49/221) of MYFEMBREE-treated women as compared to 12.2% (27/221) of  
546 placebo-treated women.

547

## 548 **6.2 Postmarketing Experience**

549

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

554

555 *Immune system disorders*: anaphylactoid reaction

556 *Skin and subcutaneous tissue disorders*: drug eruption, angioedema, urticaria

557 *Neoplasms (benign, malignant, and unspecified)*: uterine leiomyoma degeneration

558

## 559 **7 DRUG INTERACTIONS**

560

### 561 **7.1 Effect of Other Drugs on MYFEMBREE**

562

#### 563 P-gp Inhibitors

564 Co-administration of MYFEMBREE with P-gp inhibitors increases the AUC and maximum  
565 concentration ( $C_{max}$ ) of relugolix [see *Clinical Pharmacology (12.3)*] and may increase the risk of  
566 adverse reactions associated with MYFEMBREE. Avoid use of MYFEMBREE with oral P-gp  
567 inhibitors.

568

569 If use is unavoidable, take MYFEMBREE first, separate dosing by at least 6 hours, and monitor patients  
570 for adverse reactions [see *Dosage and Administration (2.4)*].

571

572 Combined P-gp and Strong CYP3A Inducers

573 Use of MYFEMBREE with combined P-gp and strong CYP3A inducers decreases the AUC and C<sub>max</sub> of  
574 relugolix, estradiol, and/or norethindrone [see *Clinical Pharmacology (12.3)*] and may decrease the  
575 therapeutic effects of MYFEMBREE. Avoid use of MYFEMBREE with combined P-gp and strong  
576 CYP3A inducers.

577

578 **8 USE IN SPECIFIC POPULATIONS**

579

580 **8.1 Pregnancy**

581

582 Pregnancy Exposure Registry

583 There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to  
584 MYFEMBREE during pregnancy. Pregnant females exposed to MYFEMBREE and healthcare  
585 providers are encouraged to call the MYFEMBREE Pregnancy Exposure Registry at 1-855-428-0707.

586 Risk Summary

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

591

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

595

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

601

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

605

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

612

613 Data

614 *Animal Data*

615 In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the  
616 period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, total litter loss, or decreased  
617 number of live fetuses at a dose of 9 mg/kg/day (about half the human exposure at the maximum  
618 recommended human dose [MRHD] of 40 mg daily, based on AUC). No treatment related  
619 malformations were observed in surviving fetuses. No treatment related effects were observed at  
620 3 mg/kg/day (about 0.1-fold the MRHD) or lower. The binding affinity of relugolix for rabbit GnRH  
621 receptors is unknown.

622  
623 In a similar embryo-fetal development study, oral administration of relugolix to pregnant rats during the  
624 period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at  
625 doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body  
626 weight gain and food consumption) was observed. A no observed adverse effect level (NOAEL) for  
627 maternal toxicity was 200 mg/kg/day (86 times the MRHD). In rats, the binding affinity of relugolix for  
628 GnRH receptors is more than 1000-fold lower than that in humans, and this study represents an  
629 assessment of non-pharmacological targets of relugolix during pregnancy. No treatment related  
630 malformations were observed up to 1000 mg/kg/day.

631  
632 In a pre- and postnatal developmental study in pregnant and lactating rats, oral administration of  
633 relugolix to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no  
634 effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose  
635 in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity  
636 was 100 mg/kg/day (34 times the MRHD).

637

## 638 **8.2 Lactation**

639

### 640 Risk Summary

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

644

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

648

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

652

### 653 Data

#### 654 *Animal Data*

655 In lactating rats administered a single oral dose of 30 mg/kg radiolabeled relugolix on post-partum day  
656 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in  
657 plasma at 2 hours post-dose.

658

659 **8.3 Females and Males of Reproductive Potential**

660

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

663

664 Pregnancy Testing

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

670

671 Contraception

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

677

678 **8.4 Pediatric Use**

679

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

681

682 **8.6 Hepatic Impairment**

683

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

688

689 **10 OVERDOSAGE**

690

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

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

695

696 **11 DESCRIPTION**

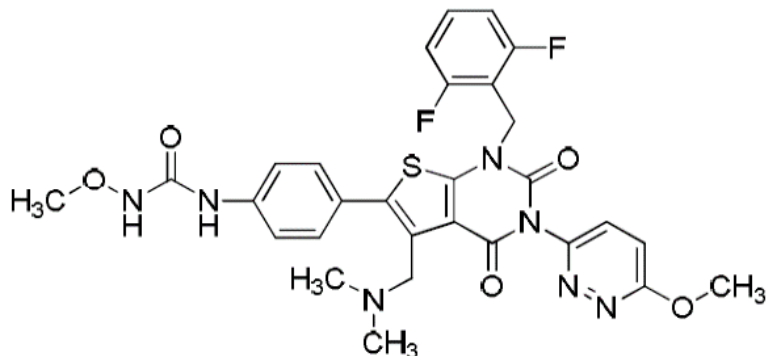
697

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

700

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

704 tetrahydrothieno[2,3-d]pyrimidin-6-yl}phenyl)-N-methoxyurea with the empirical formula of  
705  $C_{29}H_{27}F_2N_7O_5S$  and a molecular weight of 623.63. The structural formula is:  
706



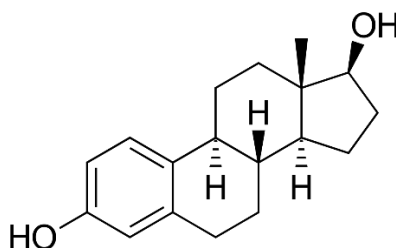
707

708

**relugolix**

709

710 Estradiol (E2), an estrogen, is present as the hemihydrate ( $C_{18}H_{24}O_2 \cdot \frac{1}{2}H_2O$ ) which is a white or almost  
711 white crystalline powder. Its chemical name is estra-1, 3, 5 (10)-triene-3, 17 $\beta$ -diol with the empirical  
712 formula of  $C_{18}H_{24}O_2$  and a molecular weight of 272.4. The structural formula is:



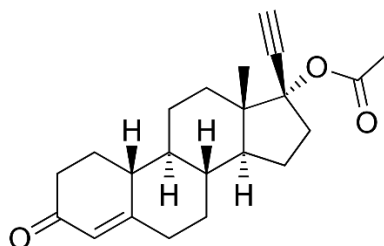
713

714

**estradiol**

715

716 Norethindrone acetate (NETA), a progestin, is a white or yellowish-white crystalline powder. Its  
717 chemical name is 17-Hydroxy-19-nor-17 $\alpha$ -pregn-4-en-20-yn-3-one acetate with the empirical formula of  
718  $C_{22}H_{28}O_3$  and a molecular weight of 340.5. The structural formula is:  
719



720

721

**norethindrone acetate**

722

723 Each MYFEMBREE (relugolix, estradiol, and norethindrone acetate) film-coated tablet contains the  
724 following inactive ingredients: hydroxypropyl cellulose, hypromellose, iron oxide yellow, lactose  
725 monohydrate, mannitol, magnesium stearate, sodium starch glycolate, titanium dioxide, and triacetin.  
726

## 727 12 CLINICAL PHARMACOLOGY

728

### 729 12.1 Mechanism of Action

730

731 MYFEMBREE is a combination of relugolix, estradiol (E2), and norethindrone acetate (NETA).

732

733 Relugolix is a non-peptide GnRH receptor antagonist that competitively binds to pituitary GnRH  
734 receptors, thereby reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone  
735 (FSH), leading to decreased serum concentrations of the ovarian sex hormones estradiol and  
736 progesterone and reduced bleeding associated with uterine fibroids and pain associated with  
737 endometriosis.

738

739 Estradiol acts by binding to nuclear receptors that are expressed in estrogen-responsive tissues. As a  
740 component of MYFEMBREE, the addition of exogenous estradiol may reduce the increase in bone  
741 resorption and resultant bone loss that can occur due to a decrease in circulating estrogen concentrations  
742 from relugolix alone.

743

744 Progestins such as norethindrone act by binding to nuclear receptors that are expressed in progesterone-  
745 responsive tissues. As a component of MYFEMBREE, norethindrone may protect the uterus from the  
746 potential adverse endometrial effects of unopposed estrogen.

747

### 748 12.2 Pharmacodynamics

749

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

- 751 • Increased thyroxin-binding globulin levels leading to *[see Warnings and Precautions (5.13)]*:
  - 752 ○ Increased circulating total thyroid hormone concentrations as measured by protein-bound  
753 iodine (PBI), thyroxine (T4) levels (by column or by radioimmunoassay), or  
754 triiodothyronine (T3) concentrations by radioimmunoassay
  - 755 ○ Decreased T3 resin uptake
  - 756 ○ Unaltered free T4 and free T3 concentrations in women with normal thyroid function  
757 *[see Warnings and Precautions (5.13)]*.
- 758 • Elevated corticosteroid-binding globulin (CBG) and sex hormone-binding globulin (SHBG)  
759 concentrations leading to increases in total circulating corticosteroid and sex hormone  
760 concentrations, respectively *[see Warnings and Precautions (5.13)]*.
- 761 • Possible decreased free testosterone concentrations.
- 762 • Possible increased other plasma proteins concentrations (angiotensinogen/renin substrate, alpha-  
763 1 antitrypsin, ceruloplasmin).
- 764 • Increased plasma high-density lipoprotein (HDL) and HDL2 cholesterol subfraction  
765 concentration, reduced low-density lipoprotein concentration, increased triglyceride  
766 concentrations.
- 767 • Accelerated prothrombin time, partial thromboplastin time, and platelet aggregation time;  
768 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 <sub>0-inf</sub> (ng·hr/mL or pg·hr/mL), mean (SD)	198.1 (111.6)	818.7 (334.4)	17.5 (8.5)
C <sub>max</sub> (ng/mL or pg/mL), mean (SD)	26.0 (18.2)	28.0 (19.2)	3.6 (1.4)
T <sub>max</sub> (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<sub>0-inf</sub> = AUC from time 0 extrapolated to infinity; C<sub>max</sub> = maximum observed concentration; E2 = estradiol; NET = norethindrone; T<sub>max</sub> = time to maximum observed concentration.

Notes: AUC<sub>0-inf</sub> is presented in ng·hr/mL for relugolix, NET and in pg·hr/mL for unconjugated E2. C<sub>max</sub> 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.

804 Absorption

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

806 Effect of Food

807 The AUC<sub>0-inf</sub> and C<sub>max</sub> of relugolix decreased by 38% and 55%, respectively, after administration of  
808 MYFEMBREE following consumption of a high-fat, high-calorie meal (i.e., 800-1000 calorie meal in  
809 which 50% of calories are derived from fat) compared with the fasted state; however, the decrease in  
810 exposure to relugolix is considered not to be clinically meaningful. No clinically meaningful effects of  
811 food on the exposure to estradiol or norethindrone were observed.

812

813 Distribution

814 Plasma protein binding of relugolix is 68% to 71%, primarily to albumin and to a lesser extent to  $\alpha_1$ -acid  
815 glycoprotein. The mean blood-to-plasma ratio is 0.78. Estradiol circulates in the blood bound to SHBG  
816 (36% to 37%) and to albumin (61%), while only approximately 1% to 2% is unbound. Norethindrone  
817 also binds to a similar extent to SHBG (36%) and to albumin (61%).

818

819 Elimination

820 After administration of a single dose of MYFEMBREE, the mean (SD) terminal phase elimination half-  
821 life (t<sub>1/2</sub>) of relugolix, estradiol, and norethindrone are 61.5 (13.2) hours, 16.6 (7.7) hours, and 10.9 (3.1)  
822 hours, respectively.

823

824 Metabolism

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

826

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

831

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

836

837 Excretion

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

840

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

843

844 Specific Populations

845 No clinically significant differences in the pharmacokinetics of relugolix were observed based on age  
846 (19 to 53 years), race/ethnicity (Asian [49%], White [24%], Black/African American [24%]), body



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

851

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

855

## 856 Drug Interaction Studies

### 857 *Clinical Studies*

858 • *Combined P-gp and Moderate CYP3A Inhibitor:* Co-administration with erythromycin (P-gp and  
859 moderate CYP3A inhibitor) increased the AUC and C<sub>max</sub> of relugolix by 6.2-fold.

860

861 • *Combined P-gp and Strong CYP3A Inducer:* Co-administration with rifampin (P-gp and strong  
862 CYP3A inducer) decreased the AUC and C<sub>max</sub> of relugolix by 55% and 23%, respectively.

863

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

869

### 870 *In Vitro Studies*

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

874

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

878

## 879 **13 NONCLINICAL TOXICOLOGY**

880

### 881 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

882

#### 883 Carcinogenesis

##### 884 *Relugolix*

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

889

##### 890 *E2/NETA*

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

893  
894 Mutagenesis

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

898 Impairment of Fertility

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

903  
904 In human GnRH-receptor knock-in mice, administration of relugolix at oral doses of 100 mg/kg and  
905 above twice daily to female mice induced a constant diestrus phase and decreased ovarian and uterine  
906 weights, effects which were reversible following cessation of treatment. In male knock-in mice, oral  
907 administration of relugolix decreased prostate and seminal vesicle weights at doses 3 mg/kg and above  
908 twice daily for 28 days, effects which were reversible, except for testis weight, which did not fully  
909 recover within 28 days after drug withdrawal.

910  
911 In a 39-week toxicology study in monkeys, a decrease in the frequency of menses was observed in  
912 female monkeys at 50 mg/kg/day (99 times the MRHD of 40 mg daily in women, based on AUC),  
913 which was partially reversed following a 13-week recovery period. There were no significant effects on  
914 male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human  
915 exposure at a dose of 120 mg daily in men, based on AUC).

916  
917 **13.2 Animal Toxicology and/or Pharmacology**

918  
919 Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues  
920 (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, GI tract or testes) after repeated  
921 oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis  
922 was observed at doses of 100 mg/kg (approximately 30 times the exposure at the MRHD of 40 mg daily  
923 in women based on AUC) and above. In a monkey 39-week toxicity study, this effect was observed at  
924 doses of 1.5 mg/kg (approximately equal to the MRHD) and above and demonstrated evidence of  
925 reversibility after cessation of treatment. The significance of this finding in humans is unknown.

926  
927 **14 CLINICAL STUDIES**

928  
929 **14.1 Heavy Menstrual Bleeding Associated with Uterine Fibroids**

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

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

934

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

937

- 938 • Subserosal, intramural, or < 50% intracavitary submucosal fibroid with a diameter  $\geq 2$  cm, or
- 939 • Multiple small fibroids with a total uterine volume of  $\geq 130\text{cm}^3$ .

940

941 Women also had to have menstrual blood loss (MBL) volume of  $\geq 80$  mL per cycle for two menstrual  
942 cycles or  $\geq 160$  mL during one cycle quantified by the alkaline hematin method from menstrual products  
943 collected during baseline menstrual cycles to be included in the studies. Women with hemoglobin  
944 < 8.0 g/dL were excluded from the study. Iron therapy was required for women with hemoglobin  
945  $\geq 8$  g/dL and  $\leq 10$  g/dL. Women were allowed, but not required, to take calcium and vitamin D during  
946 the study.

947

948 In Studies L1 and L2, women were randomized 1:1:1 to receive a once daily relugolix 40 mg tablet plus  
949 an over encapsulated tablet of E2 1 mg and NETA 0.5 mg (relugolix+E2/NETA), which is equivalent to  
950 1 tablet of MYFEMBREE, for 24 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for  
951 12 weeks followed by MYFEMBREE for 12 weeks. Treatment was initiated within the first seven days  
952 after the onset of menses.

953

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

959

960 A total of 768 women were randomized and treated in Studies L1 and L2 (741 women in the efficacy  
961 population used for these studies). Of the 741 women, 247 received treatment with MYFEMBREE (122  
962 and 125 in Studies L1 and L2, respectively), 252 received treatment with relugolix followed by  
963 MYFEMBREE (125 and 127 in Studies L1 and L2, respectively), and 242 received placebo (113 and  
964 129 in Studies L1 and L2, respectively). The median age of women included in the efficacy analysis was  
965 43 years (19 - 51 years), and mean body mass index was 31.6 kg/m<sup>2</sup>. Approximately 53% of study  
966 participants were Black, 41% were White, and 6% were of other races. Across studies at baseline, mean  
967 ( $\pm$  standard deviation) MBL volume at baseline was 231 mL ( $\pm 156$ ). Baseline uterine size in Studies L1  
968 and L2 ranged from normal to greater than 28 weeks gestation size (47 - 2625 cm<sup>3</sup>).

969

### 970 Menstrual Blood Loss

971 In both Study L1 and Study L2, a statistically higher proportion of women treated with MYFEMBREE  
972 achieved the primary endpoint of both an MBL volume of less than 80 mL and at least a 50% reduction  
973 from baseline in MBL volume over the last 35 days of treatment compared with placebo (Table 8).

974  
975

**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)
<b>Women with MBL Volume &lt; 80 mL and ≥50% Reduction in MBL Volume from Baseline to the Last 35 Days of Treatment</b>	72.1%	16.8%	71.2%	14.7%
<b>Difference from placebo, % 95% CI p-value</b>	55.3% (44.2%, 65.6%) < 0.0001		56.5% (46.6%, 66.5%) < 0.0001	

976 Abbreviations: CI = confidence interval.  
977

978 Amenorrhea

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

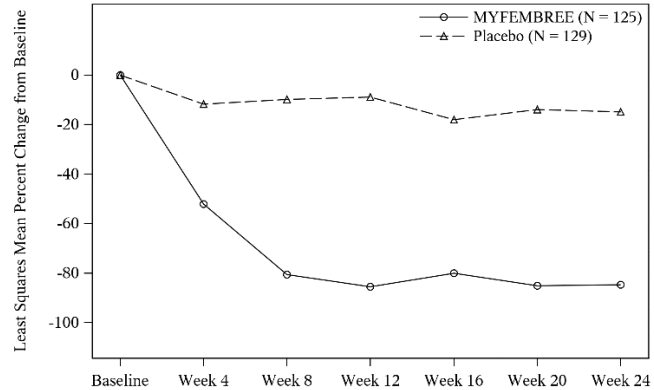
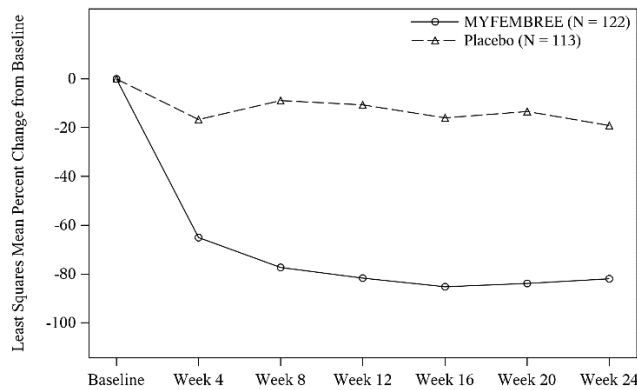
982  
983 Percent Change in MBL Volume

984 The mean MBL volumes in Studies L1 and L2 at baseline were 243.8 mL and 246.7 mL in the  
985 MYFEMBREE group and 223.2 mL and 211.8 mL in the placebo group, respectively. The mean  
986 reduction in MBL volume from baseline to Week 24 in the MYFEMBREE group was 82.0% in Study  
987 L1 and 84.3% in Study L2, which was greater than placebo (19.1% and 15.1%, respectively).  
988 Reductions in MBL volume for MYFEMBREE and placebo groups are depicted in [Figure 1](#).  
989

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

991 **Study L1**

**Study L2**



994 Hemoglobin Levels

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

999 **Table 9: Proportion of Women with Baseline Hgb ≤ 10.5 and > 2 g/dL Improvement in**  
1000 **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)
<b>% at Week 24</b>	44.2%	17.2%	55.0%	5.7%
<b>Difference from placebo, %</b>	26.9%		49.3%	
<b>95% CI</b>	(6.7%, 47.2%)		(32.7%, 66.0%)	
<b>p-value</b>	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.

1001

1002 Recurrence of Heavy Menstrual Bleeding After Discontinuation of MYFEMBREE

1003

1004 In a randomized withdrawal study (L4), 229 women from the open label extension Study L3 were  
1005 rerandomized to either continue blinded treatment with MYFEMBREE or withdrawal of therapy  
1006 (placebo) for an additional 52 weeks. The median time to return to heavy menstrual bleeding among  
1007 women randomized to placebo (treatment withdrawal) was 5.9 weeks.

1008

1009 **14.2 Moderate to Severe Pain Associated with Endometriosis**

1010 The efficacy of MYFEMBREE was assessed in two 24-week, multinational, randomized, double-blind,  
1011 placebo-controlled studies in pre-menopausal women with moderate to severe pain associated with  
1012 endometriosis in Study S1 (NCT03204318) and Study S2 (NCT03204331).

1013

1014 In Studies S1 and S2, women with moderate to severe pain associated with endometriosis were  
1015 randomized 1:1:1 to receive once daily treatment with a tablet of relugolix 40 mg plus an over  
1016 encapsulated tablet of E2 1 mg and NETA 0.5 mg, (equivalent to one tablet of MYFEMBREE) for 24  
1017 weeks, placebo for 24 weeks, or relugolix 40 mg monotherapy for 12 weeks followed by MYFEMBREE  
1018 for 12 weeks.

1019

1020 For study inclusion, women had to have endometriosis confirmed by direct visualization during surgery  
1021 and/or histology in addition to pain associated with endometriosis during a placebo run-in period.  
1022 Dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) were assessed daily using an 11-point  
1023 numerical rating scale (NRS) ranging from 0 (“no pain”) to 10 (“pain as bad as you can imagine”).  
1024 Specifically, women had to have pain that met the following criteria:

1025

- DYS NRS score  $\geq 4.0$  on at least 2 days AND
- Mean NMPP NRS score  $\geq 2.5$  or  
Mean NMPP NRS score  $\geq 1.25$  and NMPP NRS score  $\geq 5.0$  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<sup>2</sup>. 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<sup>2</sup>. 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)
<b>Dysmenorrhea</b>	74.5%	26.9%	75.1%	30.5%
Difference from placebo (95% CI) p-value	47.6% (39.3%, 56.0%) $\leq 0.0001$	-	44.6% (35.9%, 53.3%) $\leq 0.0001$	-
<b>Non-menstrual pelvic pain</b>	58.5%	39.6%	65.9%	42.5%
Difference from placebo (95% CI) * p-value	18.9% (9.5%, 28.2%) $\leq 0.0001$	-	23.4% (13.9%, 32.8%) $\leq 0.0001$	-

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.

1059

1060 Key secondary efficacy endpoints included changes from baseline in the DYS NRS scores, NMPP NRS  
1061 scores, Endometriosis Health Profile-30 (EHP-30) pain domain scores, dyspareunia NRS scores, and  
1062 opioid use.

1063

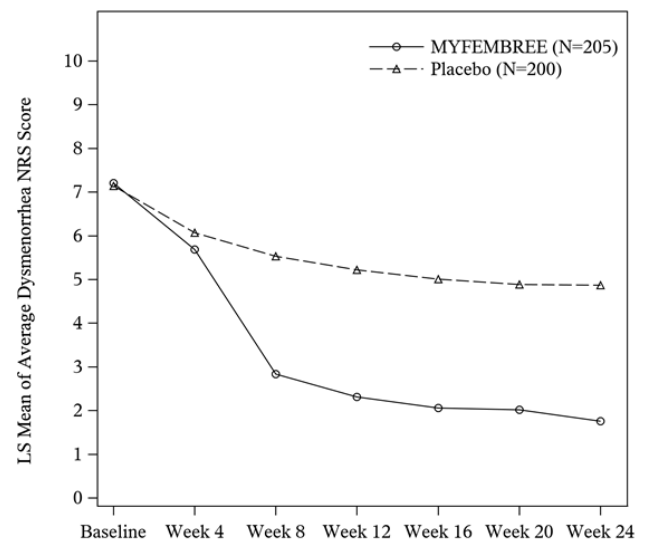
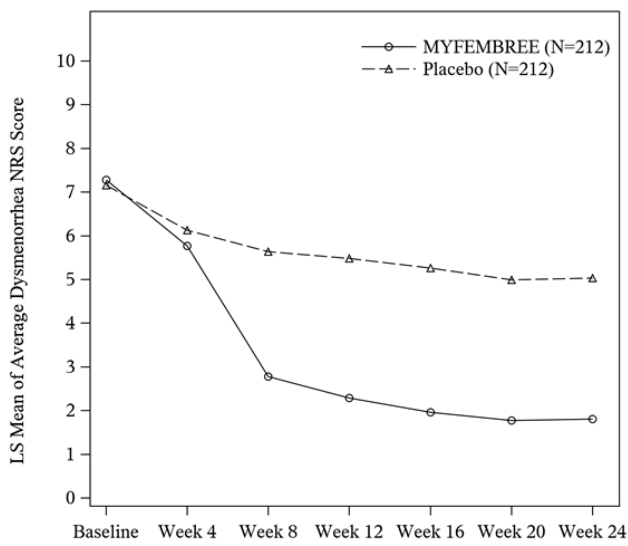
1064 Reduction in DYS and NMPP NRS Scores

1065 Women treated with MYFEMBREE had a greater reduction in DYS and NMPP NRS scores as  
1066 compared to placebo from baseline to Week 24 in both Studies S1 and S2 (Figure 2 and Figure 3).

1067 **Figure 2: Mean DYS NRS Scores in Study S1 and Study S2 over 24 Weeks**

1068 **Study S1**

**Study S2**



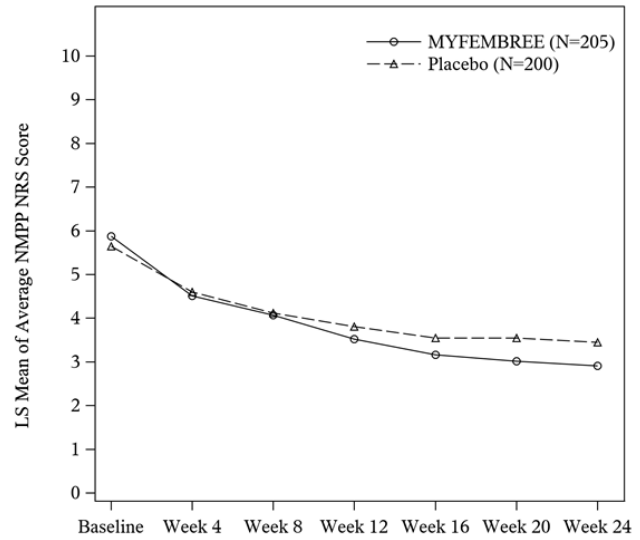
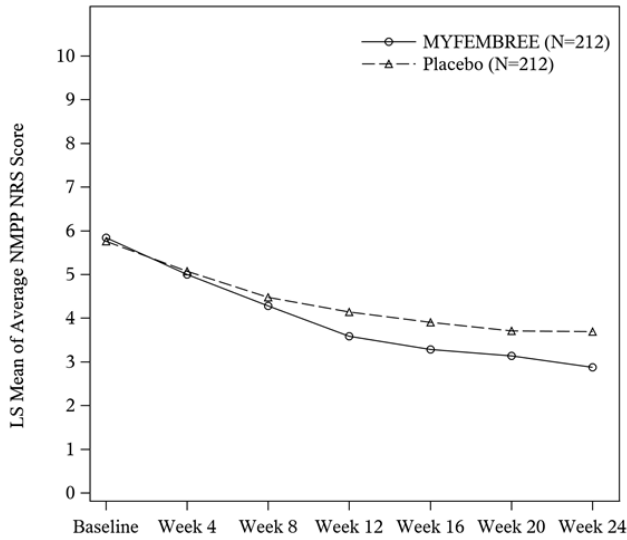
1069

1070

1071 **Figure 3: Mean NMPP NRS Scores in Study S1 and Study S2 over 24 Weeks**

1072 **Study S1**

**Study S2**



1073

1074

1075 Reduction in EHP-30 Pain Domain Scores

1076 The impact of moderate to severe pain associated with endometriosis was evaluated using the pain  
1077 domain from the Endometriosis Health Profile-30 (EHP-30), where the domain score (normalized)  
1078 ranges from 0 to 100 with a higher score representing greater impact of pain on activities.

1079

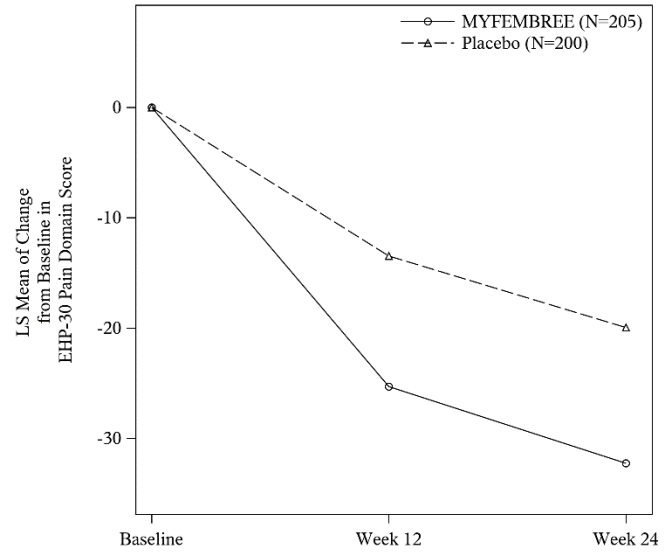
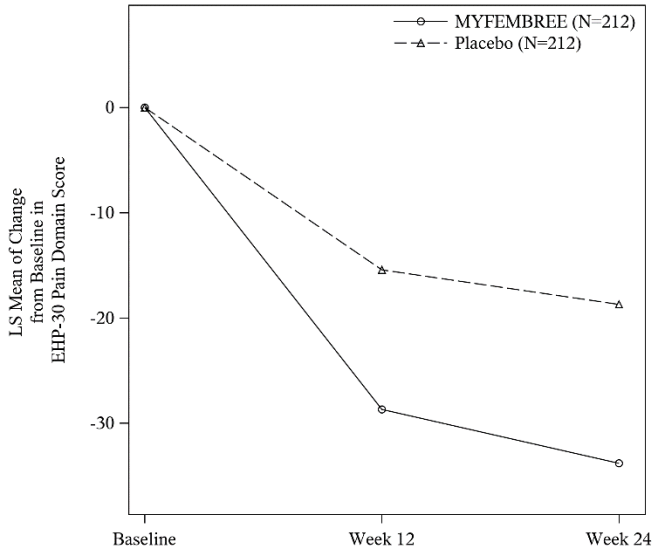
1080 Women taking MYFEMBREE reported an improvement from baseline in EHP-30 pain domain score  
1081 compared to placebo at Week 24 in both Studies S1 and S2 (Study S1: -33.8 vs. -18.7 with a treatment  
1082 difference of -15.1 [95% CI: -19.7, -10.5] and Study S2: -32.2 vs. -20.0 with a treatment difference of -  
1083 12.3 [95% CI: -16.7, -7.8]). Least squares mean changes in EHP-30 pain domain scores over time are  
1084 shown in [Figure 4](#).



1085 **Figure 4: Mean Change in EHP-30 Pain Domain Scores in Studies S1 and S2 over 24 Weeks**

1086 **Study S1**

**Study S2**



1087

1088

1089 Reduction in Dyspareunia

1090 Dyspareunia associated with endometriosis was evaluated in a subgroup of women who engaged in  
1091 sexual activity with vaginal intercourse at baseline and during treatment (68% of enrolled women).  
1092 Dyspareunia (pain during sexual intercourse) was assessed daily using an 11-point NRS ranging from 0  
1093 (“no pain”) to 10 (“pain as bad as you can imagine”). In Studies S1 and S2, women treated with  
1094 MYFEMBREE had a greater reduction in dyspareunia from baseline to Week 24 compared with placebo  
1095 [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  
1096 Study S2: -2.4 vs. -1.9, with a treatment difference of -0.5 (95% CI: -1.0, 0.0)].

1097

1098 Use of Opioid Rescue Analgesics

1099 The opioid analgesics used in the studies were tramadol 50 mg, codeine 30 mg, tramadol/acetaminophen  
1100 (TRM/APAP) 37.5/325 mg, codeine/APAP at strengths of 15/500 mg, 30/300 mg, and 30/500 mg, and  
1101 hydrocodone/acetaminophen 5/325 mg. The opioid rescue analgesics used at baseline, Month 3, and  
1102 Month 6 are shown in [Table 11](#).

1103

1104 The clinical relevance of these data has not been demonstrated.

1105 **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%)

1106 Max = maximum; Min = minimum; SD = standard deviation; monthly tablets calculations are both on 28-day interval.

1107 \* = denominator is the number of subjects on opioid rescue analgesics at baseline.

1108 # = denominator is the number of subjects off opioid rescue analgesics at baseline.

1109

1110

1111 **16 HOW SUPPLIED/STORAGE AND HANDLING**

1112

1113 **16.1 How Supplied**

1114 MYFEMBREE film-coated tablets contain relugolix 40 mg, estradiol (E2) 1 mg, and norethindrone  
1115 acetate (NETA) 0.5 mg. The tablets are light yellow to yellow, round film-coated tablet with “MVT” on  
1116 one side and “415” on the other side.

1117

1118 MYFEMBREE is supplied in a white, opaque, high-density polyethylene bottle containing 28 tablets  
1119 with desiccant and closed with an induction-sealed child-resistant cap (NDC Code 72974-415-01).

1120

1121 **16.2 Storage and Handling**

1122 Store at 15°C to 30°C (59°F to 86°F).

1123

1124 Dispose unused medication via a take-back option if available. Otherwise, follow FDA instructions for  
1125 disposing medication in the household trash, [www.fda.gov/drugdisposal](http://www.fda.gov/drugdisposal). Do NOT flush down the toilet.

1126

1127

1128 **17 PATIENT COUNSELING INFORMATION**

1129

1130 Advise the patient to read the FDA-approved patient labeling (Patient Information).

1131

1132 Thromboembolic Disorders and Vascular Events

1133 Advise patients that use of estrogen and progestin combinations may increase the risk of venous and  
1134 arterial thrombotic/thromboembolic events, especially in women at high risk for these events [*see Boxed  
1135 Warning, Contraindications (4) and Warnings and Precautions (5.1)*].

1136

1137 Bone Loss

1138 Advise patients about the risk of bone loss. Advise patients that supplementary calcium and vitamin D  
1139 may be beneficial if dietary intake of calcium and vitamin D is not adequate. Advise women that oral  
1140 iron supplementation should not be taken at the same time as calcium and vitamin D [*see Warnings and  
1141 Precautions (5.2) and Adverse Reactions (6.1)*].

1142

1143 Suicidal Ideation and Mood Disorders (Including Depression)

1144 Advise patients that depression, mood disorders, and suicidal ideation may occur with MYFEMBREE  
1145 use. Instruct women with new onset or worsening depression, anxiety, or other mood changes to  
1146 promptly seek medical attention [*see Warnings and Precautions (5.4) and Adverse Reactions (6.1)*].

1147

1148 Hepatic Impairment and Transaminase Elevations

1149 Advise women to promptly seek medical attention in case of signs or symptoms that may reflect liver  
1150 injury, such as jaundice [*see Warnings and Precautions (5.5)*].

1151

1152 Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

1153 Advise patients that MYFEMBREE may delay the recognition of pregnancy because it may reduce the  
1154 duration and amount of menstrual bleeding. Advise patients to use effective non-hormonal  
1155 contraception while taking MYFEMBREE and to discontinue MYFEMBREE if pregnancy is  
1156 diagnosed [*see Warnings and Precautions (5.8)*]. Advise pregnant patients that there is a pregnancy  
1157 registry that monitors pregnancy outcomes in women exposed to MYFEMBREE during pregnancy [*see  
1158 Use in Specific Populations (8.1, 8.3)*].

1159

1160 Alopecia

1161 Advise women with uterine fibroids that alopecia, hair loss, and hair thinning in no specific pattern may  
1162 occur with MYFEMBREE. Advise these women that hair loss and hair thinning may not resolve  
1163 completely after stopping MYFEMBREE. Advise these women to contact their healthcare provider if  
1164 they have concerns about changes to their hair [*see Warnings and Precautions (5.11) and Adverse  
1165 Reactions (6.1)*].

1166

1167 Females of Reproductive Potential

1168 Advise women to use effective non-hormonal contraception while taking MYFEMBREE and for one  
1169 week after discontinuing treatment and to discontinue MYFEMBREE if pregnancy is confirmed.

1170 Advise pregnant patients that there is a pregnancy registry that monitors pregnancy outcomes in women  
1171 exposed to MYFEMBREE during pregnancy [*see Use in Specific Populations (8.1, 8.3)*].

1172

1173 Drug Interactions

1174 Advise women to report their use of any other prescription or nonprescription medications or dietary  
1175 supplements. Co-administration with certain drugs may decrease the therapeutic effects of  
1176 MYFEMBREE [*see Drug Interactions (7.1)*].

1177

1178 Administration Instructions

- 1179 • Advise women to begin taking MYFEMBREE as soon as possible after the start of menses but  
1180 no later than 7 days after menses has started [*see Dosage and Administration (2.2)*].
- 1181 • Advise women to take any missed dose of MYFEMBREE as soon as possible the same day  
1182 and then resume regular dosing the next day at the usual time [*see Dosage and Administration*  
1183 *(2.3)*].
- 1184 • Advise women taking oral P-gp inhibitors to take MYFEMBREE first and separate dosing by at  
1185 least 6 hours [*see Dosage and Administration (2.4)*].

1186

1187

1188 Manufactured by Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9, Canada

1189 Distributed by: Sumitomo Pharma America, Inc., 84 Waterford Drive, Marlborough, MA 01752

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## 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 moodPay 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](http://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](http://www.MYFEMBREE.com)



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