Relugolix, Estradiol, Norethindrone (MYFEMBREE)
National Drug Monograph
March 2024

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Relugolix is a gonadotropin releasing hormone receptor (GnRH) antagonist that competitively binds to GnRH receptors in the pituitary gland and inhibits endogenous GnRH signaling. Relugolix reduces the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which leads to reduced concentrations of ovarian sex hormones estradiol and progesterone.
- In the MYFEMBREE product, relugolix is combined with estradiol to decrease the bone loss that occurs with relugolix alone and norethindrone to protect the uterus from adverse endometrial effects of unopposed estrogen.

Indication(s) Under Review in This Document

- Management of heavy menstrual bleeding (HMB) associated with uterine leiomyomas (fibroids) in premenopausal women (FDA approved May 2021)
- Management of moderate to severe pain associated with endometriosis in premenopausal women (FDA approved August 2022)
- *Note: Relugolix is also FDA approved as a single agent in a higher dose for the management of advanced prostate cancer (not included in this review).*

Dosage Form(s) Under Review

- Oral tablets in a fixed-dose combination containing 40 mg relugolix, 1 mg estradiol (E2), 0.5 mg norethindrone acetate (REN)
- Dose regimen: One tablet orally daily at the same time each day
- Treatment duration should be limited to 24 months due to the risk of bone loss that may not be reversible.
- Prior to starting treatment, exclude pregnancy and discontinue hormonal contraceptives.

Clinical Evidence Summary

Efficacy Considerations

HMB associated with uterine leiomyomas (fibroids)[1,2,3,4,5]

- FDA approval of REN was based on two identically designed, international, randomized, double-blind, placebo-controlled, industry sponsored 24-week phase 3 trials (LIBERTY-1 and LIBERTY-2) that evaluated the efficacy of REN in reducing HMB and other symptoms of fibroids. Additional evidence supporting use includes the LIBERTY extension trial (totaling 52 weeks of treatment) and then a withdrawal study.

- LIBERTY-1 and LIBERTY-2 enrolled premenopausal women between 18 and 50 years of age who had ultrasound confirmed diagnosis of fibroids and HMB. HMB was assessed by the alkaline hematin method and defined as menstrual blood loss volume of 80 ml or more per cycle for two cycles or 160 ml or more during one cycle. Key exclusion criteria were low bone mineral density (BMD) (z-score less than -2.0 at the lumbar spine, total hip, or femoral neck), other causes for HMB, and hormonal therapy.

- Patients were randomized to one of three arms: REN for 24 weeks, placebo for 24 weeks, or relugolix monotherapy for 12 weeks followed by REN for 12 weeks (delayed REN arm). The delayed REN arm was included in the trial to be able to compare BMD and vasomotor symptoms between REN and relugolix monotherapy in the first 12 weeks. The primary efficacy endpoint was the percent of responders in the REN vs. placebo group. Response was defined as a volume of menstrual blood loss of less than 80 ml and a reduction from baseline of at least 50% in menstrual blood loss volume (over the last 35 days of treatment period).

- Baseline: A total of 388 patients in LIBERTY-1 and 382 patients in LIBERTY-2 underwent randomization, and 79% of patients in each of the trials completed treatment. Baseline characteristics between all groups were similar (see Table 1). Overall demographics: mean age 42 years; 51% Black; 43% White; mean body mass index (BMI) 32.

- Results: Significantly more patients in the REN group achieved a response in the reduction of menstrual blood loss compared to placebo in both trials. Improvements were seen by week 4 and sustained throughout the 24-week study period. Maximum effect was seen at 8 weeks. REN was associated with improvements in several key secondary endpoints (see Table 2). No significant improvement in the largest fibroid volume was found with REN.

- In a single-arm, 28-week extension of the LIBERTY trial (n=477), effectiveness of REN was sustained for the 52-week duration of treatment.

- In the LIBERTY randomized, placebo-controlled withdrawal study (n=229), continuation of REN for up to 104 weeks of treatment was associated with maintenance of reduction in menstrual blood loss. Most patients relapsed when treatment was stopped, with return of HMB at a median of 6 weeks after discontinuation.

Table 1: Selected Baseline Characteristics LIBERTY-1 and LIBERTY-2: Fibroids

Characteristic	LIBERTY-1		LIBERTY-2	
	REN N=128	PBO N=127	REN N=125	PBO N=129
Menstrual blood loss (mL)	239	218	247	212
Pts with menstrual blood loss ≥225 mL (%)	34	33	36	33
Hemoglobin (g/dL)	11.2	11.4	11.3	11.1
Pts with Hgb ≤10.5 g/dL (%)	23	18	25	29
Bleeding and pelvic discomfort scale score (mean)	67	71	71	70
Pts with max NRS score for uterine fibroid-associated pain ≥4 (%)	66	75	74	74

Bleeding and pelvic discomfort scale score = evaluates 3 symptoms (heavy bleeding, passing clots, and pelvic discomfort) with higher scores indicating more severe symptoms; Hgb=hemoglobin NRS=numerical rating scale (0 = no pain to 10 = worst pain); Hgb=hemoglobin

Table 2: Selected Efficacy Results LIBERTY-1 and LIBERTY-2

Endpoint	LIBERTY-1		LIBERTY-2	
	REN N=128	PBO N=127	REN N=125	PBO N=129
Primary – Pts with menstrual blood loss reduction (%)	73	19	71	15
Difference from PBO (%)	54		57	
Pts with amenorrhea – (%)	52	6	50	3
Change in menstrual blood loss volume (baseline to wk 24) (%)	84	23	84	15
Change in bleeding and pelvic discomfort scale score (baseline to wk 24)	-45	-16	-52	-18
Pts with baseline anemia and increased Hgb >2 g/dL at 24 wks (%)	50	22	61	5
Pts in baseline pain subgroup with NRS score of ≤1 in last 35 days (%)	43	10	47	17
Change from baseline to wk 24 in uterine volume (%)	2	-13	-1.5	-14

All comparisons vs. placebo <0.05; Bleeding and pelvic discomfort scale score = evaluates 3 symptoms (heavy bleeding, passing clots, and pelvic discomfort) with higher scores indicating more severe symptoms. Response = 20 points or greater improvement; numerical rating scale = 0 (no pain) to 10 (worst pain); Hgb=hemoglobin

***Moderate to Severe Pain with Endometriosis*[1,6,7]**

- The efficacy of REN for FDA approval in the treatment of endometriosis pain was evaluated in two identically designed, international, randomized, double-blind, placebo-controlled, industry sponsored 24-week phase 3 trials (SPIRIT-1 and SPIRIT-2).

- SPIRIT-1 and SPIRIT-2 enrolled women aged 18 to 50 years with endometriosis (confirmed by surgery and/or histology) along with moderate to severe pain associated with endometriosis during a placebo run-in period defined as:
    - Dysmenorrhea Numerical Rating Scale (DYS NRS) score ≥ 4 on at least 2 days AND
    - Nonmenstrual pelvic pain score (NMPP NRS) mean of ≥ 2.5 or a mean of ≥ 1.25 with scores ≥ 5 on at least 4 days.

- Key exclusion criteria were low BMD (z-score less than -2.0 at the lumbar spine, total hip, or femoral neck), history of non-endometriosis pelvic pain, or contraindication to hormonal therapy.

- After a 30-day placebo run-in period, patients were randomized to one of three arms: REN for 24 weeks, placebo for 24 weeks, or relugolix monotherapy for 12 weeks followed by REN for 12 weeks (delayed REN arm). The delayed REN arm was included in the trial to be able to compare BMD and vasomotor symptoms between REN and relugolix monotherapy in the first 12 weeks. The co-primary efficacy endpoints were portion of responders based on the DYS NRS score and NMPP NRS score at week 24.

- Baseline: A total of 638 patients in SPIRIT-1 and 623 patients in SPIRIT-2 underwent randomization, and 84% and 81% of patients in each of the trials completed treatment, respectively. Overall demographics: mean age 34 years; 91% White, 6% Black; 21% North America; mean BMI 26. (See Table 3)

- Results: For the co-primary endpoints, significantly more patients in the REN group achieved a response as measured by a reduction in DYS NRS score and NMPP NRS score vs. placebo in both trials. Improvements were seen in dysmenorrhea by 8 weeks and in nonmenstrual pelvic pain by 12 weeks. Effects were sustained through 24 weeks for both endpoints (see Table 4). REN was associated with improvements in several key secondary endpoints. Results from the single arm extension study suggest that effectiveness of REN was sustained at 52 weeks and 104 weeks (unpublished; NCT 03654274).

Table 3. Selected Baseline Characteristics SPIRIT-1 and SPIRIT-2: Endometriosis

Characteristic	SPIRIT-1		SPIRIT-2	
	REN N=212	PBO N=212	REN N=206	PBO N=204
DYS NRS score (mean)	7.2	7.1	7.1	7.0
≥7 (%)	60	58	55	53
NMPP NRS score (mean)	5.9	5.8	5.8	5.5
≥4 (%)	80	80	80	78
Opioid analgesic use (%)	30	26	49	47

DYS=dysmenorrhea; NMPP=nonmenstrual pelvic pain; NRS=numerical rating scale (0 = no pain to 10 = worst pain)

Table 4. Selected efficacy results SPIRIT-1 and SPIRIT-2: Endometriosis

Endpoint	SPIRIT-1		SPIRIT-2	
	REN	PBO	REN	PBO
Co-Primary Endpt – Pt responders based on DYS NRS score (%)*	75	27	75	30
Difference from PBO (%)	48		45	
Co-Primary Endpt – Pt responders based on NMPP NRS score (%)*	59	40	66	43
Difference from PBO (%)	19		23	
Change in DYS NRS score	-5.1	-1.8	-5.1	-2.0
Change in NMPP NRS score	-2.9	-2.0	-2.7	-2.0
Pts not using opioids during treatment (%)	86	76	82	66

Change in dyspareunia NRS (subgroup)	-2.4	-1.7	-2.0	-1.9

P < 0.05 for REN vs. PBO comparisons; *thresholds for responders for DYS NRS = -2.8 and for NMPP NRS = -2.1
DYS=dysmenorrhea and no increased analgesics in last 35 days of treatment; NMPP=nonmenstrual pelvic pain; NRS=numerical rating scale (0 = no pain to 10 = worst pain)

Safety Considerations[1,2,3,4,5,6]

Safety Results from Clinical Trials

- Safety data used to support original FDA approval of REN were based on LIBERTY-1, LIBERTY-2, the LIBERTY open-label extension study, as well as data from the endometriosis and prostate cancer clinical development programs and postmarketing data from relugolix monotherapy in Japan.
- Many of the adverse effects are related to the suppression of estrogen and progesterone induced by relugolix including hot flushes, reduced bone mineral density (BMD), depression and other mood disorders, and risk of pregnancy loss.
- As a GnRH antagonist combination product with estrogen and progestin, REN carries the same contraindications and warnings of other estrogen and progestin combinations.

- **Boxed warning for thromboembolic disorders and vascular events**
  - Estrogen and progestin combinations increase the risk of thrombotic or thromboembolic events including deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, and myocardial infarction (MI), especially in women at increased risk for these events.
  - One patient receiving REN in the clinical trials for endometriosis experienced DVT and PE.

- **Contraindications (includes contraindications for estrogens and progestins):**
  - Pregnancy
  - Known osteoporosis
  - Known hepatic impairment or hepatic disease
  - High risk of arterial, venous thrombotic, or thromboembolic disorder
  - Current or history of breast cancer or other hormone-sensitive malignancies
  - Undiagnosed abnormal uterine bleeding
  - Known hypersensitivity to ingredients

- **Other warnings / precautions:**
  - ***Bone loss***
    - REN may cause bone loss in some patients and may not be completely reversible after stopping treatment. Bone loss may be greater with longer durations of use.
    - Baseline assessment of BMD by DXA is recommended. Follow-up DXA is recommended annually during REN treatment for endometriosis and periodically during REN treatment for fibroids.

- Calcium and vitamin D supplementation may be beneficial for patients with inadequate intake, but this was not studied.
- HMB associated with fibroids: Add-back therapy with estrogen and progestin mitigated BMD loss associated with REN compared to the relugolix monotherapy group at 12 wks. At 52 weeks, REN was associated with a loss of BMD at the lumbar spine of -0.8% without a clear plateau. A greater than 3% loss of BMD at the lumbar spine was found in 23% of REN patients. The extent of BMD recovery after discontinuing treatment is unknown. Additional data are available for a small number of patients who received REN for a total of 104 weeks and suggested that BMD was generally preserved (in selected patients who did not have significant bone loss on REN in the earlier trials).
- Endometriosis: At 52 weeks, REN was associated with a loss of BMD at the lumbar spine of -0.8%. A greater than 3% loss of BMD at the lumbar spine was found in 20% of REN patients. There was one low trauma fracture reported in the extension study in a patient treated with relugolix monotherapy followed by REN.

- ***Suicidal ideation and mood disorders (including depression)***
  - GnRH antagonists including REN have been associated with adverse mood disorders including depression and suicidal ideation, particularly in patients with history of mood disorders.
  - Evaluate patients with history of mood disorders and/or suicidal ideation before initiating treatment. Monitor for mood changes and depressive symptoms after initiating treatment and determine if continued treatment benefits outweigh the risks. Advise patients to seek immediate medical attention for suicidal ideation and behavior.

- ***Elevated blood pressure:*** New or worsening hypertension occurred more frequently with REN vs. placebo in clinical trials for HMB associated with fibroids. REN is contraindicated in patients with uncontrolled hypertension. Monitor blood pressure in patients with controlled hypertension.

- ***Uterine fibroid prolapse or expulsion:*** Cases of uterine fibroid prolapse and expulsion were reported with REN during clinical trials. Women with submucosal uterine fibroids should be advised about possible prolapse or expulsion and to seek medical attention if severe bleeding or cramping occurs while on REN.

- ***Alopecia:*** Alopecia was reported more frequently with REN compared to placebo in the HMB associated with fibroids trials as well as with other GnRH antagonists. It is unknown if the alopecia is reversible. Consider discontinuation if hair loss becomes a concern.

- ***Change in menstrual bleeding patterns (and reduced ability to recognize pregnancy):*** REN should be initiated as soon as possible and within 7 days after the start of menses. If REN is initiated later in the menstrual cycle, irregular and/or heavy bleeding may

initially occur. Over time, REN may cause amenorrhea or a reduction in menstrual bleeding duration or intensity which may delay the ability to recognize pregnancy. If pregnancy is suspected, perform pregnancy test, and discontinue REN if confirmed.

- ***Early pregnancy loss***
- ***Hypersensitivity reactions:*** Hypersensitivity including anaphylactoid reactions, urticaria, and angioedema have been reported with REN.
- ***Standard warnings for estrogen and progestin combinations***

- **Adverse reactions - HMB associated with fibroids**

Table 5. Common adverse reactions occurring more frequently with REN and >3%

LIBERTY-1 and LIBERTY-2 (pooled data)	REN N=254 %	PBO N=256 %
Vasomotor symptoms	10.6	6.6
Hypertension	4.7	1.6
Abdominal pain	3.5	1.6
Alopecia	3.5	0.8
Decreased libido	3.1	0.4

- **Serious adverse events:** menorrhagia, fibroid prolapse/expulsion, and pelvic pain
- **Deaths:** none
- **Discontinuations due to adverse events:** 3.9% REN vs. 4.3% PBO

- **Adverse reactions – Endometriosis**

Table 6. Common adverse reactions occurring more frequently with REN and >5%

SPIRIT-1 and SPIRIT-2 (pooled data)	REN N=418 %	PBO N=416 %
Headache	33.0	26.4
Vasomotor symptoms	13.2	7.2
Mood disorders	9.1	7.2
Abnormal uterine bleeding	6.7	4.6
Nausea	6.0	4.1
Toothache	5.5	2.4

- **Serious adverse events:** uterine hemorrhage, suicidal ideation, cholelithiasis, cholecystitis
- **Deaths:** none

- **Discontinuations due to adverse events:** 4.5% REN vs. 2.9% PBO

Other Considerations[1]

- **Pregnancy**
  - REN is contraindicated in pregnancy. Based on animal studies and the mechanism of action, exposure to REN early in pregnancy may cause early pregnancy loss. Insufficient human data are available to determine whether there is an increased risk for major birth defects or miscarriage.
  - Menstrual changes related to REN may reduce the ability of women to recognize pregnancy.
  - Exclude pregnancy before initiating REN and perform pregnancy testing during treatment if pregnancy is suspected. Discontinue REN if pregnancy is confirmed.
- **Contraception:** Advise women to use effective non-hormonal contraception during treatment with REN and for one week after discontinuation. Avoid concomitant use of estrogen-containing hormonal contraceptives as estrogen-related adverse effects may occur, and effectiveness of relugolix may be reduced.
- **Drug interactions:**
  - Avoid use of REN with oral-P-glycoprotein (P-gp) inhibitors due to potential increased relugolix exposure and adverse reactions. If unavoidable, take the interacting drug at least 6 hours after REN.
  - Avoid use of REN with combined strong P-gp and CYP3A inducers due to potential decreased REN exposure and reduced effectiveness.
- **Return of menses:** Based on patients who stopped REN in the LIBERTY and SPIRIT trials, most women resume menses in about 30 to 40 days.
- **Lactation:** It is unknown whether relugolix is excreted in human breast milk. Estrogen and progestin have been found in breast milk and can reduce milk production. Consider risks and benefits of the infant and lactating patient.

Other Therapeutic Options

Alternative treatments for endometriosis are listed in tables 7 and 8 below

Table 7. Treatment alternatives for uterine leiomyoma

Drug	VANF status	Considerations
GnRH Antagonist		
Relugolix, estradiol, norethindrone (MYFEMBREE)	TBD	• Oral pill; once daily • Max duration 24 mos
Elagolix, estradiol, norethindrone (ORIAHNN)	NF	• Oral pill; twice daily • Max duration 24 mos
GnRH Agonist		
Leuprolide (LUPRON DEPOT)	NF	• IM depot injection – 3.75 mg monthly or 11.25 mg every 3 mos • Max duration 3 mos • Used pre-op to improve anemia

Table 8. Treatment alternatives for endometriosis

Drug	VANF status	Considerations
GnRH Antagonist		
Relugolix, estradiol, norethindrone (MYFEMBREE)	TBD	• Oral pill once daily • Max duration 24 mos
Elagolix 150 mg (ORILISSA)	NF	• Oral pill once daily • Max duration 24 mos • Partial estrogen suppression
Elagolix 200 mg (ORILISSA)	NF	• Oral pill twice daily • Max duration 6 mos • Near full estrogen suppression • Higher dose effective for dyspareunia
GnRH Agonist		
Goserelin (ZOLADEX)	NF	• SQ implant – 3.6 mg every 28 days • Max duration 6 mos • Estrogen suppression to menopausal levels
Leuprolide (LUPRON DEPOT)	NF	• IM depot injection – 3.75 mg monthly or 11.25 mg every 3 mos • Max duration 12 mos (6 mos + 6 mos retreatment) • Estrogen suppression to menopausal levels
Nafarelin (SYNAREL)	NF	• Nasal spray administered twice daily • Max duration 6 mos

Projected Place in Therapy

HMB associated with uterine leiomyoma

- Uterine fibroids are common in reproductive age females, with up to 70% developing fibroids before age 50. Fibroids occur more frequently in Black compared to White females and are symptomatic in about 25% of individuals. Fibroids may be associated with HMB, anemia, bulk symptoms, pelvic pain, infertility, and decreased quality of life.[8]
- Management depends on the patient's type and severity of symptoms and short- and long-term goals. Treatments may include surgical, procedural, or pharmacologic interventions. Medications approved for fibroid-related bleeding issues are leuprolide and elagolix (combined with estradiol and norethindrone). In addition to reducing HMB, leuprolide reduces leiomyoma size and uterine volume and is often used a bridge prior to surgery. Oral tranexamic acid is indicated to reduce HMB (without a specific indication for fibroids). Hormonal contraceptives and levonorgestrel-bearing intrauterine devices (IUDs) are used off-label to treat HMB with or without fibroids.
- REN is the second oral GnRH antagonist/estrogen/progestin combination approved for HMB associated with uterine leiomyoma. Use is limited to a maximum duration of 2 years due to concerns for bone loss.
- There is moderate quality evidence supporting the efficacy of REN in reducing menstrual blood loss (84% reduction from baseline), which appears to be sustained through 52 weeks and 104 weeks of treatment. Since REN was compared to placebo rather than active treatment alternatives, the place in therapy is unclear.
- The overall safety profile of REN is notable for risk of bone loss, mood disorders including suicidal ideation, early pregnancy loss, hot flushes, and the additional risks associated with estrogen and progestins. Use of add-back therapy (estrogen plus progestin) appears to lessen bone loss and improve overall tolerability.

Moderate to Severe Pain in Endometriosis

- Endometriosis is a chronic condition that affects 6 to 10% of women of reproductive age.
- Treatment with a GnRH agonist or antagonist is generally reserved for patients with more severe or recurrent symptoms and/or who don't respond to other treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and hormonal contraceptives.
- GnRH agonists (leuprolide, goserelin, nafarelin) induce a hypoestrogenic state and are associated with related adverse effects such as hot flushes, vaginal dryness, mood swings, BMD loss, etc. Bone loss limits the duration of therapy with GnRH analogs. Add-back therapy with norethindrone acetate reduces bone loss and may improve overall tolerability. Leuprolide and goserelin are injections given in monthly or 3-monthly (leuprolide) formulations. Nafarelin is a nasal spray administered twice daily.
- Relugolix is the second oral GnRH antagonist combination approved for moderate to severe pain in endometriosis. Use of REN is limited to a maximum duration of 2 years due to concerns for bone loss.
- Elagolix was the first oral GnRH antagonist FDA approved for endometriosis. Elagolix is available as a single agent tablet in 2 different doses and produces a dose dependent hypoestrogenic state. Elagolix was shown to be effective compared to placebo. The lower dose of elagolix is

approved for a maximum treatment duration of 24 months. High dose elagolix is effective in relieving dyspareunia but is limited to a 6 month treatment duration.

- Incidence of mood disorders was higher in patients with a history of mood disorders, which may be particularly important when considering use in the Veteran population, given the higher baseline presence of mental health conditions.

References

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