LABEL NAME	MANUFACTURER	DRUG TYPE	PROVIDER SYNERGIES BRAND NAME ROUTE
MYFEMBREE 40 MG-1 MG-0.5 MG TB	MYOVANT SCIENCE	SSB	MYFEMBREE (ORAL)
ORIAHNN 300-1-0.5MG/300MG CAPS	ABBVIE US LLC	SSB	ORIAHNN (ORAL)
ORILISSA 150 MG TABLET	ABBVIE US LLC	SSB	ORILISSA (ORAL)
ORILISSA 200 MG TABLET	ABBVIE US LLC	SSB	ORILISSA (ORAL)

Relugolix/Estradiol Hemihydrate/Norethindrone Acetate (Myfembree®) Drug Bulletin

June 2021

Nonproprietary Name	relugolix/estradiol hemihydrate/norethindrone acetate
Brand Name	Myfembree
Manufacturer	Myovant Sciences
FDA Approval Date	May 26, 2021
Market Availability Date	June 2021
Indication	Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women *Limitation of use:* Use should be limited to 24 months due to the risk of continued bone loss which may not be reversible
Dosage Form	Fixed dose oral tablet (relugolix 40 mg/estradiol 1 mg/norethindrone acetate 0.5 mg)
Dosage	1 tablet once daily at approximately the same time, with or without food; start as early as possible after the onset of menses but no later than 7 days after menses has started

CLINICAL CONSIDERATIONS

- Myfembree is a combination of 3 agents: *relugolix*, a gonadotropin-releasing hormone (GnRH) antagonist that binds to pituitary GnRH receptors and reduces hormones and bleeding associated with uterine fibroids; *estradiol*, exogenous estrogen that counteracts the loss of estrogen from relugolix; and *norethindrone acetate*, a progestin necessary for women with a uterus who are on estrogen.[1]
- Safety[2]
  - Contraindications – women with a high risk of arterial, venous thrombotic, or thromboembolic disorders, including women > 35 years of age who smoke or have headaches with focal neurological symptoms or migraine headaches with aura as well as women who are known to have current or history of deep vein thrombosis or pulmonary embolism, vascular disease, thrombogenic valvular or thrombogenic rhythm diseases of the heart, inherited or acquired hypercoagulopathies, or uncontrolled hypertension; pregnancy; osteoporosis; current or history of breast cancer or other hormone-sensitive malignancies; hepatic impairment or

disease; undiagnosed abnormal uterine bleeding; or known anaphylactic reaction, angioedema, or hypersensitivity.

- Boxed warning – thromboembolic disorders and vascular events
- Other warnings – bone loss; history of or current hormonally-sensitive malignancies (e.g., breast cancer); depression, mood disorders, and suicidal ideation; hepatic impairment and transaminase elevations; gallbladder disease or cholestatic jaundice history; increased blood pressure; menstrual bleeding changes and decreased ability to recognize pregnancy; risk of early pregnancy loss; uterine fibroid prolapse or expulsion; alopecia; increased blood glucose, cholesterol, or triglycerides; laboratory result effects (e.g., reduction in free thyroid or corticosteroid hormone levels); and hypersensitivity
- Common Adverse Reactions (≥ 3% and higher than placebo; reported as incidence versus placebo) – hot flush, hyperhidrosis, or night sweats (10.6% versus 6.6%); abnormal uterine bleeding (6.3% versus 1.2%); alopecia (3.5% versus 0.8%); and libido decreased (3.1% versus 0.4%)
- Drug Interactions – concurrent administration with P-glycoprotein (P-gp) inhibitors increases the AUC and C_{max} of relugolix and should be avoided; however, the products can be taken 6 hours apart and the patient should be monitored for adverse reactions; combination therapy with P-gp and strong CYP3A inducers reduces the AUC and C_{max} of all components thereby reducing effectiveness

- Special Populations[3]
  - Pregnancy – may increase risk of early pregnancy loss; contraindicated in pregnancy; women with reproductive potential should use effective non-hormonal contraception during treatment and for 1 week following treatment discontinuation
  - Pediatrics – safety/effectiveness not established in < 18 years of age
  - Hepatic Impairment – contraindicated with hepatic impairment; increased exposure to estradiol and its associated adverse reactions
- Clinical Trials[4]
  - Approved via the 505(b)(2) pathway
  - **LIBERTY 1** (L1; NCT03049735) and **LIBERTY 2** (L2; NCT03103087), replicate international, randomized, double-blind, placebo-controlled, 24-week, phase 3 studies, studied the safety and efficacy of relugolix combination therapy (relugolix + estradiol + norethindrone acetate) in women 18 to 50 years of age (L1 [n=388] and L2 [n=382]) with an ultrasound-confirmed diagnosis of fibroids causing heavy menstrual bleeding of ≥ 80 mL per cycle for 2 cycles or a volume of ≥ 160 mL during 1 cycle. Pregnant patients, patients with a history of osteoporosis or objective signs of low bone density, patients with other causes of heavy menstrual bleeding, or were using hormonal therapy were excluded. Patients were randomized 1:1:1 to once-daily placebo for 24 weeks, relugolix combination therapy for 24 weeks, or delayed relugolix combination therapy (relugolix monotherapy, followed by relugolix combination therapy, each

for 12 weeks). The primary endpoint in both trials was menstrual blood loss (measured by the alkaline hematin method over the last 35 days of the treatment period) of < 80 mL and a ≥ 50% reduction in menstrual blood loss from baseline during the final month; comparison being the percentage of patients who responded to relugolix combination therapy versus placebo. The median age of the included patients was 42.5 years, and 50% of the patients included were White while 46% were Black. A higher percentage of patients who received relugolix combination therapy met the primary endpoint ([73% in L1; 71% in L2] compared to placebo [19% in L1; 15% in L2]; p<0.001 for both studies) which was similar to the delayed relugolix combination therapy groups (80% in L1; 73% in L2; p<0.001). The overall incidence of adverse events was higher in the delayed relugolix combination therapy group, while the incidences in the relugolix combination therapy group and placebo group were similar; hot flashes were the most common adverse effect in both trials. Changes in bone mineral density (BMD) were similar in the relugolix combination therapy group and the placebo group, but in the delayed relugolix combination therapy group, BMD decreased with relugolix monotherapy.

- Uterine fibroids, or uterine leiomyomas, are the most common benign gynecologic tumors and result in overgrowth of connective tissue and smooth muscle in the uterus. The incidence is common, occurring in approximately 50% to 60% of all women of reproductive age especially from age 35 to 49 years, with the risk increasing with age. In addition, uterine fibroids are more likely to affect Black or African American women compared to White or Caucasian women or Asian women. Uterine fibroids generally resolve following menopause.[5]
- According to The American College of Obstetricians and Gynecologists (ACOG), most women affected by uterine fibroids are asymptomatic and require no treatment; however, when symptomatic, treatment should focus on symptom management. Treatment selection, including possible surgical intervention or embolization, is based on the woman's preference for uterine preservation and future fertility. Pharmacologic therapies include oral contraceptives (Level C recommendation) and levonorgestrel-releasing intrauterine devices (Level B recommendation) to help reduce menorrhagia, and GnRH agonists with or without add-back therapy (Level A recommendation) to shrink the fibroids. Tranexamic acid (Lysteda®) is approved for the treatment of cyclic heavy menstrual bleeding and may also be considered for treatment (Level B recommendation). Regarding GnRH antagonists with add-back therapy specifically, ACOG states these may be considered for up to 2 years (Level B recommendation).[6]
- Relugolix/estradiol hemihydrate/norethindrone acetate (Myfembree) is the 2nd GnRH antagonist for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. ACOG recommends Myfembree as a Level B recommendation due to limited or inconsistent evidence. It is a direct competitor to elagolix/estradiol/norethindrone acetate (Oriahnn®), and the length of treatment for both agents is limited to 24 months due to irreversible bone loss. Although they have not been studied in a head-to-head trial, Myfembree appears comparable to Oriahnn, and ACOG gives them the same level of recommendation (Level B); the exception being that Myfembree is dosed once daily compared to twice daily Oriahnn.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Pituitary Suppressive Agents, LHRH
Clinical Edit	**Initial Approval Criteria** ▪ Patient age is ≥ 18 years; **AND** ▪ Patient is premenopausal; **AND** ▪ Patient has confirmed diagnosis of uterine leiomyomas (fibroids) with heavy menstrual bleeding; **AND** ▪ Myfembree is prescribed by, or in consultation with, a specialist in gynecology or reproductive health; **AND** ▪ Patient has failed (or has a contraindication to) an adequate trial of 1 of the following therapies: – Combination hormonal contraceptives; **OR** – Progestins (including oral or transdermal formulations, vaginal ring, intrauterine device, or injections); **OR** – Tranexamic acid; **AND** ▪ Pregnancy is excluded prior to initiating treatment (within 7 days from the onset of menses); **AND** ▪ Patient will use effective non-hormonal contraception during treatment with Myfembree and 1 week after stopping therapy; **AND** ▪ Patient does NOT have osteoporosis (defined as a Z score less than -2.0 at lumbar spine, total hip, or femoral neck); **AND** ▪ Patient does not have hepatic impairment (Child-Pugh A, B, or C) or disease; **AND** ▪ Patient does NOT have any of the following contraindications to Myfembree treatment: – Known hypersensitivity to the active or inactive ingredients; **OR** – High risk of arterial, venous thrombotic, or thromboembolic disorders, including the following: ▪ Smokers > 35 years of age; **OR** ▪ Current or history of deep vein thrombosis or pulmonary embolism; **OR** ▪ Vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular disease); **OR** ▪ Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease, or atrial fibrillation); **OR** ▪ Inherited or acquired hypercoagulopathies; **OR** ▪ Uncontrolled hypertension; **OR** ▪ Headaches with focal neurological symptoms or have migraine headaches with aura if > 35 years of age; **OR**

Suggested Utilization Management (continued)

Clinical Edit *(continued)*	**Initial Approval Criteria *(continued)*** – Current or history of breast cancer or other hormone-sensitive malignancies, and with increased risk for hormone-sensitive malignancies; **OR** – Undiagnosed abnormal uterine bleeding. **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Prescriber attestation that patient has had clinically meaningful response to treatment; **AND** ▪ Prescriber attestation that the patient does not have osteoporosis and provides the Z score (patient should not have a Z score less than -2.0 at lumbar spine, total hip, or femoral neck); **AND** ▪ Patient has not experienced any treatment-restricting adverse effects (e.g., decreased bone density, hepatic impairment, thromboembolic disorders and vascular events, mood disorders/suicidal ideation).
Quantity Limit	28 tablets/28 days
Duration of Approval	Initial: 12 months Renewal: 12 months (maximum total duration of 24 months)
Drug to Disease Hard Edit	Known hypersensitivity; osteoporosis; liver impairment or disease; high risk arterial, venous thrombotic, or thromboembolic disorders (e.g., female smokers > 35 years of age, uncontrolled hypertension, headache with focal neurological symptoms or migraines with aura and > 35 years [see prescribing information for additional examples]); pregnancy; history of or current hormonally-sensitive malignancies (e.g., breast cancer); undiagnosed abnormal uterine bleeding

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Elagolix/Estradiol/Norethindrone Acetate; Elagolix (Oriahnn™) Abbreviated New Drug Update (ANDU)

June 2020

OVERVIEW[1]

- Indication – elagolix/estradiol/norethindrone acetate capsules co-packaged with elagolix capsules (Oriahnn) is indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women
  - Due to the risk of continued bone loss (which may not be reversible), limit use to 24 months
  - Elagolix is a gonadotropin-releasing hormone (GnRH) receptor antagonist, estradiol is an estrogen, and norethindrone acetate is a progestin
- Contraindications/Warnings
  - Contraindications – known hypersensitivity, osteoporosis, liver impairment or disease; high risk arterial, venous thrombotic, or thromboembolic disorders (e.g., female smokers > 35 years of age, uncontrolled hypertension, headache with focal neurological symptoms or migraines with aura and > 35 years [see prescribing information for additional examples]); pregnancy; history of or current hormonally-sensitive malignancies (e.g., breast cancer); undiagnosed abnormal uterine bleeding; and use with organic anion transporting polypeptide (OATP)1B1 inhibitors known or expected to increase elagolix exposure to a clinically significant extent
  - Boxed warning – thromboembolic disorders and vascular events
  - Other warnings – bone loss, suicidal ideation or behavior/mood disorders, hepatic impairment/transaminase elevations, increased blood pressure, menstrual bleeding changes/decreased ability to recognize pregnancy, allergic reactions secondary to inactive components (e.g., FD&C Yellow No 5 [tartrazine]), gallbladder disease/cholestatic jaundice history, alopecia, carbohydrate and lipid metabolism effects (e.g., increased glucose, changed in lipid levels), laboratory result effects (e.g., select thyroid or corticosteroid levels)
  - Exclude pregnancy prior to initiation, within 7 days from the onset of menses; women should use non-hormonal contraception during treatment and for 1 week following discontinuation
- Drug Interactions
  - Elagolix is a weak to moderate cytochrome P450 3A (CYP3A) inducer, a weak 2C19 inhibitor, and inhibits the P-glycoprotein (P-gp) efflux pump. Oriahnn can impact the following agents:
    - CYP3A substrates (e.g., midazolam) – dose increase may be needed

        - CYP2C19 substrates (e.g., omeprazole) – avoid omeprazole doses > 40 mg/day
        - P-gp substrates (e.g., digoxin) – increase monitoring
        - Rosuvastatin – monitor lipid levels
    - Elagolix is a substrate of CYP3A, P-gp, and OATP1B1; estradiol and norethindrone acetate are CYP3A substrates. The following agents may impact the effects of Oriahnn:
        - Strong CYP3A inducers – decreased Oriahnn efficacy; do not use with rifampin
        - Strong CYP3A inhibitors – increased Oriahnn exposure; avoid use
        - OATP1B1 inhibitors – increased Oriahnn exposure; contraindicated
- Common Adverse Effects (≥ 5% and higher than placebo; reported as incidence versus placebo) – hot flush (22% versus 9%), headache (9% versus 7%), fatigue (6% versus 4%), and metrorrhagia (5% versus 1%).
- Special Populations
    - Pregnancy – may increase risk of early pregnancy loss; contraindicated in pregnancy
    - Pediatrics – safety/effectiveness not established in < 18 years of age
    - Hepatic Impairment – contraindicated with any degree of hepatic impairment or disease due to estradiol-related adverse effects and increased elagolix exposure
    - Renal impairment – no dose adjustment required in any degree of renal impairment, including end-stage renal disease and dialysis
- Availability – co-packaged; carton containing 4 weekly blister packs containing 7 morning capsules and 7 evening capsules
    - Morning capsules contain elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg
    - Evening capsules contain elagolix 300 mg
- Dosages – 1 elagolix/estradiol/norethindrone acetate capsule in the morning and 1 elagolix capsule in the evening, at approximately the same time each day, with or without food, for up to 24 months
- Clinical Trials[2]
    - Two replicate, randomized, double-blind, double-dummy, placebo-controlled, multinational, 6-month, phase 3 studies assessed the safety and efficacy of Oriahnn for the management of heavy menstrual bleeding (HMB) associated with uterine fibroids in 790 premenopausal women (Elaris UF-1 [n=412] and Elaris UF-2 [n=378]). These trials included patients ages 18 to 51 years with ultrasound-confirmed diagnosis of uterine fibroids and > 80 mL of menstrual blood loss per cycle for ≥ 2 menstrual separate cycles. Pregnant patients and those with persistent or complex ovarian cyst, cancer, pelvic inflammatory disease, or a history of osteoporosis or objective signs of low bone density were excluded. Patients were randomized within 10 days of the start of menses 2:1:1 to elagolix 300 mg twice daily with estradiol 1 mg and norethindrone acetate 0.5 mg once daily, elagolix 300 mg twice daily alone, or placebo. The trials consisted of a washout period (if applicable), a screening period, a 6-month treatment period, and a 12-month follow-up period or extension study. The primary endpoint in both trials was menstrual blood loss (measured by the alkaline hematin method) of < 80 mL and a ≥

50% reduction in menstrual blood loss from baseline during the final month. Several other endpoints were assessed. The median age of the included patients was 43 years, and a majority of the patients included were Black or African American (68%), while 29% were White or Caucasian. A higher percentage of women who received elagolix/estradiol/norethindrone acetate met the primary endpoint (68.5% in UF-1; 76.5% in UF-2) compared to placebo (8.7% in UF-1; 10% in UF-2); $p<0.001$ for both studies. The primary endpoint was met in 84.1% in UF-1 and 77% in UF-2 with elagolix alone. Statistically significant differences from placebo were also found in both trials in volume of menstrual blood loss at multiple time points and the final month, suppression of bleeding during the final month, and in women with baseline hemoglobin ≤ 10.5 g/dL and an increase from baseline of > 2 g/dL at 6 months. Compared to placebo, adverse events occurred more often in the elagolix alone group in UF-1 ($p<0.001$) and the elagolix/estradiol/norethindrone acetate group in UF-2 ($p<0.05$). Hot flushes occurred more commonly in both treatment groups compared to placebo. Notably, the percent change from baseline in bone mineral density (BMD) in lumbar spine, total hip, and femoral neck was statistically decreased in the elagolix alone group compared to placebo and elagolix/estradiol/norethindrone acetate in UF-1, and the percent change from baseline in BMD in lumbar spine and total hip was statistically decreased in the elagolix alone group compared to placebo and elagolix/estradiol/norethindrone acetate in UF-2 (not statistically significant in the femoral neck in UF-2). The percent change from baseline in BMD in lumbar spine, total hip, and femoral neck was not statistically different from placebo in the elagolix/estradiol/norethindrone acetate in both trials.

CLINICAL CONSIDERATIONS[3,4,5,6]

- Uterine fibroids, or uterine leiomyomas, are the most common benign gynecologic tumors and result for overgrowth of connective tissue and smooth muscle in the uterus. These affect approximately 50% to 60% of all women of reproductive age, with the risk increasing with age. In addition, uterine fibroids are more likely to affect Black or African American women, with a 2- to 3-fold greater risk compared to White or Caucasian women; they can affect > 80% of Black or African American women by the age of 50 years. Uterine fibroids generally resolve following menopause.
- According to The American College of Obstetricians and Gynecologists (ACOG), most women affected by uterine fibroids are asymptomatic and require no treatment unless rapid growth is observed or there are other reasons to suspect pelvic malignancy. However, fibroids can cause symptoms including menstrual irregularities (intermenstrual bleeding or menorrhagia), progressive pelvic pressure, pelvic pain, back pain, frequent urination or difficulty urinating, constipation, and distortion of the uterine or abdominal wall. Uterine fibroids may affect fertility and may prolapse or degenerate causing acute onset pelvic pain.
- Treatment goals focus on the management of symptoms. Treatment selection is based, in part, on the woman's preference and desire for uterine preservation and future fertility. Surgical treatment includes myomectomy (removing the myomas with reconstruction and preservation of the uterus), hysterectomy, and uterine artery embolization (UAE). Medical therapies include oral contraceptives and progestin-releasing intrauterine devices (IUDs) to help reduce menorrhagia, non-steroidal anti-

inflammatory drugs (NSAIDs) for pain management, and mifepristone and GnRH agonists to shrink the fibroids. GnRH analogues are associated with bone loss and vasomotor symptoms. Per ACOG's guidelines, low-dose "add-back" regimens (equivalent to menopausal hormone therapy) may be initiated if a GnRH agonist is used for > 6 months to minimize these adverse effects. Current guidelines have not fully addressed the role of GnRH antagonists; however, ACOG states they may be beneficial. For general uterine bleeding management, in addition to combination and progestin-only contraceptives, ACOG also includes tranexamic acid as a treatment option. Tranexamic acid (Lysteda®) is approved for the treatment of cyclic heavy menstrual bleeding, is dosed 3 times daily, and given for a maximum of 5 days during monthly menstruation.

- Approved on May 29, 2020, Oriahnn is the first GnRH antagonist-containing product approved for patients with uterine fibroids. It offers a co-packaged treatment option of a GnRH antagonist (elagolix) and "add-back" therapy (estradiol and norethindrone acetate) as a nonsurgical option for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women. Abbvie launched Oriahnn in June 2020.
- Abbvie also manufactures elagolix (Orilissa®), which is approved for the management of moderate to severe pain associated with endometriosis.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Pituitary Suppressive Agents, LHRH
Clinical Edit	**Initial Approval Criteria** ▪ Patient age is ≥ 18 years; **AND** ▪ Patient is premenopausal; **AND** ▪ Patient has confirmed diagnosis of uterine leiomyomas (fibroids) with heavy menstrual bleeding; **AND** ▪ Oriahnn is prescribed by, or in consultation with, a specialist in gynecology or reproductive health; **AND** ▪ Patient has failed (or has a contraindication to) an adequate trial of one of the following therapies: – Combination hormonal contraceptives; **OR** – Progestins (including oral or transdermal formulations, vaginal ring, intrauterine device, or injections); **OR** – Tranexamic acid; **AND** ▪ Pregnancy is excluded prior to initiating treatment (within 7 days from the onset of menses); **AND** ▪ Patient will use effective non-hormonal contraception during treatment with Oriahnn and 1 week after stopping therapy; **AND** ▪ Patient does NOT have osteoporosis (defined as a Z score > -1.5 at spine and femur [total hip]); **AND** ▪ Patient does not have hepatic impairment (Child-Pugh A, B, or C) or disease; **AND**

Suggested Utilization Management (continued)

Clinical Edit *(continued)*	**Initial Approval Criteria *(continued)*** ▪ Patient is not on concomitant strong organic anion transport polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine, gemfibrozil) or on rifampin; **AND** ▪ Patient does NOT have any of the following other contraindications to Oriahnn treatment: – Known hypersensitivity to the active or inactive ingredients (e.g., elagolix, estradiol, norethindrone acetate, FD&C Yellow No 5); **OR** – High risk of arterial, venous thrombotic, or thromboembolic disorders, including the following: ▪ Smokers > 35 years of age; **OR** ▪ Current or history of deep vein thrombosis or pulmonary embolism; **OR** ▪ Vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular disease); **OR** ▪ Thrombogenic valvular or thrombogenic rhythm diseases of the heart (e.g., subacute bacterial endocarditis with valvular disease, or atrial fibrillation); **OR** ▪ Inherited or acquired hypercoagulopathies; **OR** ▪ Uncontrolled hypertension; **OR** ▪ Headaches with focal neurological symptoms or have migraine headaches with aura if > 35 years of age. **Renewal Criteria** ▪ Patient must continue to meet the above criteria; **AND** ▪ Prescriber attestation that patient has had clinically meaningful response to treatment; **AND** ▪ Prescriber attestation that the patient does not have osteoporosis and provide the Z score (patient should not have a Z score > -1.5 at spine and femur [total hip]); **AND** ▪ Patient has not experienced any treatment-restricting adverse effects (e.g., decreased bone density, hepatic impairment, thromboembolic disorders and vascular events, mood disorders/suicidal ideation).
Quantity Limit	1 carton/28 days
Duration of Approval	Initial: 12 months Renewal: 12 months (maximum total duration of 24 months)
Drug to Disease Hard Edit	Known hypersensitivity; osteoporosis; liver impairment or disease; high risk arterial, venous thrombotic, or thromboembolic disorders (e.g., female smokers > 35 years of age, uncontrolled hypertension, headache with focal neurological symptoms or migraines with aura and > 35 years [see prescribing information for additional examples]); pregnancy; history of or current hormonally-sensitive malignancies (e.g., breast cancer); undiagnosed abnormal uterine bleeding; use with organic anion transporting polypeptide (OATP)1B1 inhibitors

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Elagolix (Orilissa™) New Drug Update

August 2018

Drug Name:	**elagolix**
Trade Name (Manufacturer):	**Orilissa (Abbvie)**
Form:	Oral tablet
Strength:	150 mg and 200 mg
FDA Approval:	July 24, 2018
Market Availability:	Available
FDA Approval Classification:	Priority review
Classification:	LHRH (GnRH) Antagonist, Pituitary Suppressant Agents (P1N)

INDICATION[1]

Elagolix is indicated for the management of moderate to severe pain associated with endometriosis.

PHARMACOLOGY

Elagolix is a gonadotropin-releasing hormone (GnRH) receptor antagonist that binds to GnRH receptors in the pituitary gland and causes a dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), ultimately resulting in a decrease in estradiol and progesterone concentrations in the blood.

CONTRAINDICATIONS/WARNINGS

Elagolix is contraindicated in women who are pregnant, with known osteoporosis, severe hepatic impairment, or on concurrent therapy with a strong organic anion transporting polypeptide (OATP) 1B1 inhibitor (e.g., cyclosporine, gemfibrozil).

Elagolix is associated with a dose-dependent decrease in bone mineral density (BMD); therefore, limit the duration of use to reduce the degree of bone loss. Supplementing with calcium and vitamin D may provide benefit, although this has not been studied.

Women treated with elagolix may experience reduced amount, intensity, or duration of menstrual bleeding that may cause onset of pregnancy to go unnoticed. If pregnancy is suspected, a pregnancy test should be performed and if positive, elagolix should be discontinued due to risk of early pregnancy loss.

In clinical trials, elagolix was associated with an increased risk of depression, particularly in patients with a history of depression. Mood changes and suicidal ideation and behavior were also reported. Patients with depressive symptoms should promptly be evaluated to determine the benefit of continued elagolix treatment.

Dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range have been reported with elagolix. The lowest effective dose should be prescribed and patients should seek prompt medical attention if symptoms of jaundice occur. Benefit of continued therapy should be assessed.

Estrogen-containing contraceptives may reduce the efficacy of elagolix; however, the effect of progestin-only contraceptives is unknown. Women should use non-hormonal contraceptives during elagolix treatment and for 1 week after stopping therapy.

DRUG INTERACTIONS

Elagolix is a weak to moderate inducer of CYP3A and an inhibitor of efflux transporter P-glycoprotein (P-gp). Concurrent use of substrates of either protein may alter plasma concentrations of the substrate.

Elagolix is also a substrate of CYP3A, P-gp, and OATP1B1. Concurrent use of elagolix with a strong CYP3A inhibitor should be limited to 6 months for the 150 mg once daily dose, and is not recommended with the 200 mg twice daily dose. Concurrent use of elagolix with a strong CYP3A inducer may decrease elagolix plasma concentrations. Concomitant use of elagolix with an OATP1B1 inhibitor can lead to increased elagolix concentrations and use with a strong OATP1B1 inhibitor (e.g., cyclosporine, gemfibrozil) is contraindicated.

Rifampin may increase elagolix exposure; therefore, concurrent use should be limited to 6 months for the 150 mg once daily dose, and is not recommended with the 200 mg twice daily dose. Dose increases of midazolam or rosuvastatin should be considered if prescribed to patients treated with elagolix. Clinical monitoring is recommended for digoxin if co-administered with elagolix.

COMMON ADVERSE EFFECTS

The most common adverse effects reported ≥ 10% in clinical studies for the 150 mg once daily and 200 mg twice daily dosages were: hot flushes/night sweats (24% and 46%, respectively), headache (17% and 20%, respectively), and nausea (11% and 16%, respectively).

In a blinded extension study, during 12 months of continuous elagolix use, the percentage of subjects with > 8% BMD loss in lumbar spine, total hip, or femoral neck was 8% with 150 mg once daily and 21% with 200 mg twice daily dose.

A phase-2, double-blind, study, after 24 weeks of treatment, the mean percentage change from baseline in BMD for spine and femur (total hip) were small and comparable for oral elagolix 150 mg once daily (-0.11% for spine, -0.47% for femur) and subcutaneous depot medroxyprogesterone 104 mg administered at weeks 1 and 12 (-0.99% for spine, -1.29% for femur).[2]

SPECIAL POPULATIONS

Pregnancy

Use of elagolix may increase the risk of early pregnancy loss and is contraindicated in pregnant women. Data is insufficient to determine a risk for major birth defects, miscarriage, milk production, or on the effects of a breastfed child. Pregnancy should be ruled out prior to starting elagolix and women should be instructed to use effective non-hormonal contraception during and for 1 week after stopping elagolix therapy.

Pediatrics

The safety and efficacy of elagolix has not been established in patients < 18 years of age.

Hepatic Impairment

No dosage adjustment is required in the presence of mild hepatic impairment (Child-Pugh A). The dose should be limited to 150 mg once daily for a duration no more than 6 months in women with moderate impairment (Child-Pugh B). Elagolix is contraindicated with severe hepatic impairment (Child-Pugh C).

Renal Impairment

No dose adjustment is necessary with any degree of renal impairment.

DOSAGES

In women with no coexisting conditions the recommended dosage is 150 mg once daily for up to 24 months; in women who experience dyspareunia (painful intercourse) the recommended dose is 200 mg twice daily for up to 6 months. In women with moderate hepatic impairment (Child-Pugh B), 150 mg once daily for up to 6 months is recommended.

The dose should be taken at approximately the same time each day and can be taken without regard to food.

The lowest effective dose should be used and the duration of treatment should be limited to restrict the degree of bone loss.

Pregnancy should be ruled out prior to starting elagolix, or the drug should be started within 7 days of onset of menses.

CLINICAL TRIALS[3,4]

A literature search was performed using "elagolix" and "endometriosis."

Efficacy of elagolix was evaluated in 2 similar double-blind, placebo-controlled trials (Elaris Endometriosis [EM] I and II) involving 1,686 premenopausal women, 18 to 49 years of age, with a surgical diagnosis of endometriosis and moderate to severe endometriosis-related pain. Women were excluded if they had a Z score < -1.5 for BMD at the lumbar spine, femoral neck, or total hip or clinically significant gynecologic conditions or chronic pain not related to endometriosis. The trials consisted of 4 periods: (1) a washout of hormonal therapies; (2) up to a 100 day screening period, including 2 menstrual cycles, when the women were switched from their usual analgesic agents to the allowed rescue analgesia of naproxen 500 mg and/or an opioid; (3) a 6-month treatment period; and (4) a follow-up period up to 12 months (unless the women was enrolled in the 6-month extension trial). Women were randomized (2:2:3) to receive elagolix 150 mg once daily (lower dose), elagolix 200 mg twice daily (higher dose), or placebo. A total of 1,285 women completed treatment. The primary efficacy endpoints were the proportion of women who experienced a clinical response regarding dysmenorrhea and non-menstrual pelvic pain at 3 months. Each endpoint measurement was based on a pain score ranging from 0 (no pain) to 3 (severe pain) and a decrease or stabilization of rescue analgesia use. In Elaris EM-I, the clinically meaningful threshold for mean change from baseline, as compared with placebo, was -0.81 for dysmenorrhea and -0.36 for non-menstrual pelvic pain; in Elaris EM-II these values were -0.85 and -0.43, respectively. At 3 months, the percentage of women in Elaris EM-I with a clinically meaningful reduction in dysmenorrhea and decreased or stable use of rescue analgesic agents was 46.4% in the lower-dose

group and 75.8% in the higher-dose group, as compared with 19.6% in the placebo group; in Elaris EM-II, these percentages were 43.4%, 72.4%, and 22.7%, respectively ($p<0.001$ for all comparisons in both trials). Regarding reduction in non-menstrual pelvic pain and decreased/stable use of rescue analgesia at 3 months, in Elaris EM-I, the proportion of women with clinically meaningful response in the respective groups was 50.4%, 54.5%, and 36.5%, and in Elaris EM-II, these values were 49.8%, 57.8%, and 36.5% ($p\leq0.003$ for all comparisons in both trials). Effects of elagolix for both primary endpoints were maintained at 6 months and for 12 months in extension trials. Dose-dependent effects, such as hot flushes, elevated serum lipids, and decreased BMD, occurred. At 6 months, more women treated with elagolix had lumbar spine Z-scores ≤ −1.5; and the proportion of women was greater with the higher dose of elagolix (3.3% and 4.9%) compared with the lower dose (1.1% and 0.6%) or placebo (0.4% and 0%).

OTHER DRUGS USED FOR CONDITION[5,6,7]

Initial treatments for endometriosis include non-steroidal anti-inflammatory drugs (NSAIDs) and continuous hormonal birth control. Alternatives include progestins (in women who cannot take hormonal birth control), oral androgens (danazol), and GnRH agonists, such as nafarelin nasal spray (Synarel®) and injectable leuprolide (Lupron®) and goserelin (Zoladex®). GnRH agonists are effective in treating endometriosis and are associated with hot flushes, insomnia, and bone loss. Addition of an oral aromatase inhibitors (e.g., letrozole, anastrozole) may provide benefit.

PLACE IN THERAPY[8,9]

Endometriosis affects up to 10% of females aged 15 to 49 years. Elagolix is an orally administered GnRH antagonist. It reduces estrogen production and results in the shrinking of endometrial lesions.

Existing therapies may interfere with contraception and/or may be associated with unwanted hypoestrogenic adverse effects, such as reduced BMD. While GnRH agonists reduce pain in over 80% of cases, they may cause flare of endometriosis pain in the days following the dose, which is typically alleviated with concurrent hormonal (add-back) therapy. Surgery to remove scar tissue may relieve pain and improve fertility; however, symptoms often recur within 1 year.

Elagolix is the first new oral treatment option for the treatment of endometriosis to be approved by the United States (US) Food and Drug Administration (FDA) in over a decade and lacks the hormonal flare response that is observed with GnRH agonists.

The Institute for Clinical and Economic Review (ICER) has published a final review of the use of elagolix for the treatment of endometriosis. To ensure prudent use of elagolix, they state that it is reasonable for insurers to develop prior authorization criteria based on clinical evidence since there are no long-term comparative safety and efficacy data for the product. Regarding pharmacologic treatment, they suggest in premenopausal women, if adequate improvement in endometriosis symptoms is not seen after a 3-month trial of an NSAID and hormonal contraceptive, then a second-line therapy is appropriate. Since comparative data supporting the efficacy and safety of elagolix over an GnRH agonist is lacking, a trial of an GnRH prior to elagolix may be considered. Moreover, step therapy should consider factors such as time needed for reversibility of side effects, mode of administration, and duration of action. ICER further suggests requirement of prescribing by or on consultation with an obstetrics/gynecology or reproductive specialist. A limited initial coverage period of 6 months is reasonable due to potential side effects.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	N/A
Clinical Edit	Prior authorization will be required if the product is determined to be non-preferred. **Initial Criteria:** ▪ Patient age is ≥ 18 years; **AND** ▪ Patient has confirmed diagnosis of endometriosis; **AND** ▪ Patient has failed an adequate trial of the following therapies: o non-steroidal anti-inflammatory drugs (NSAIDs), **AND** o hormonal contraceptives (including oral or transdermal formulations, vaginal ring, or intrauterine device), **AND** o gonadotropin-releasing hormone (GnRH) agonist (e.g., nafarelin [Synarel®], leuprolide [Lupron®], goserelin [Zoladex®]) ▪ Elagolix is prescribed by or in consultation with an obstetrics/gynecology or reproductive specialist; **AND** ▪ Pregnancy is excluded prior to initiating treatment; **AND** ▪ Patient will use effective non-hormonal contraception during treatment with elagolix and 1 week after stopping therapy; **AND** ▪ Patient does not have osteoporosis as evident by a Z score > -1.5 at spine and femur (total hip); **AND** ▪ Patient does not have severe hepatic impairment (Child-Pugh C); **AND** ▪ Patient is not on concomitant strong organic anion transport polypeptide (OATP) 1B1 inhibitor (e.g., cyclosporine, gemfibrozil) **Renewal Criteria:** ▪ Patient continues to meet the initial criteria; **AND** ▪ Patient is considered to have clinically meaningful response to treatment
Quantity Limit	150 mg tablet: 30 tablets/30 days 200 mg tablet: 60 tablets/30 days
Duration of Approval	150 mg tablet: Initial = 6 months; Renewal = 18 months. Maximum *total* duration of 24 months 200 mg tablet: Initial = 6 months; no renewal
Drug to Disease Hard Edit	None

REFERENCES

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3 Orilissa [package insert]. North Chicago, IL; Abbvie. July 2018.
4 Taylor HS, Giudice LC, Lessey BA, et al. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. NEJM. 2017;377:28-40. DOI: 10.1056/NEJMoa1700089.
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