Elagolix, Estradiol, Norethindrone (ORIAHNN)
Mini-Monograph
March 2024

VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA National Formulary Committee drug monographs is to provide a focused drug review for making formulary decisions. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA APPROVAL	**Description/MOA**	Elagolix is a gonadotropin releasing hormone receptor (GnRH) antagonist that causes dose-dependent reductions in ovarian estradiol and progesterone and reduces bleeding associated with uterine fibroids. ORIAHNN combines elagolix with estradiol and norethindrone (EEN) (add-back therapy) to decrease bone loss and improve tolerability.
	Indication(s) Under Review	▪ **Management of heavy menstrual bleeding (HMB) associated with uterine leiomyomas (fibroids) in premenopausal women (May 2020).** ▪ *Of note, elagolix monotherapy is also approved in two doses for the treatment of moderate to severe pain in endometriosis. This indication was previously reviewed by PBM and not included in this review.*
	Dosage Form(s)	▪ Dose is one oral capsule taken twice daily packaged in weekly blister packs: o Morning dose capsule: elagolix 300 mg, estradiol 1 mg, norethindrone 0.5 mg o Evening dose capsule : elagolix 300 mg

CLINICAL EVIDENCE	**Studies/Design**	Two identically designed, double-blind, placebo-controlled, industry-sponsored 6-month trials to evaluate efficacy and safety of EEN for HMB associated with fibroids (Elaris Uterine Fibroids – UF-1 and UF-2) plus extension trial for up to 12 months of treatment
	Population	Eligible patients were premenopausal women 18 to 51 years old with ultrasound-confirmed diagnosis of uterine fibroids and HMB defined as > 80 ml menstrual blood loss per cycle for ≥ 2 cycles.
	Demographics/ baseline	N=412 (UF-1); N=378 (UF-2); Mean age: 42 yrs; Black 67%; mean menstrual blood loss/cycle: 247 mL (UF-1) and 236 mL (UF-2); mean Hgb: 11 gm/dL; pts with Hgb ≤ 10.5 g/dL 40% (UF-1) and 26% (UF-2); completed treatment: 80% (UF-1) and 77% (UF-2)
	Intervention	Patients were randomized 2:1:1 to EEN, placebo, or elagolix alone. The elagolix monotherapy arm was included to compare hypoestrogenic effects between elagolix and EEN groups.
	Results	**UF-1 and UF-2: EEN vs. PBO** ($p < 0.05$ for all comparisons) ▪ **Primary endpt % responders*:** 69% vs. 9% (UF-1) and 77% vs. 10% (UF-2) ▪ **Selected secondary endpoints:** amenorrhea 48% vs. 4% (UF-1) and 53% vs. 5% (UF-2), improvement in anemia 62% vs. 16% (UF-1) and 50% vs. 21% (UF-2) ▪ **UF-EXTENSION** study suggested EEN effects maintained for up to 12 mos
	Summary	EEN was more effective than placebo at reducing menstrual blood loss. Effects appear to be maintained through 12 months of treatment. Improvements in other secondary endpoints were observed. The overall safety profile of EEN 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.

*Defined as menstrual blood loss of < 80 ml and at least a 50% reduction from baseline to the final month.

SAFETY	**Contraindications**	High risk of arterial, venous thrombotic, or thromboembolic disorders, pregnancy, known osteoporosis, current or history of breast cancer or other hormonally sensitive malignancies, known hepatic impairment or disease, undiagnosed abnormal uterine bleeding, known anaphylactic reaction to EEN, concomitant use of organic anion transporting polypeptide (OATP)1B1 inhibitors (e.g., cyclosporine, gemfibrozil)
	Boxed Warnings	Risk of thromboembolic disorders and vascular events
	Warnings/ Precautions	Bone loss, suicidal ideation and exacerbation of mood disorders, transaminase elevations, elevated blood pressure, change in menstrual bleeding pattern and reduced ability to recognize pregnancy, alopecia, allergy to FD&C Yellow No. 5, and additional standard warnings for estrogen and progestin
	Adverse Reactions	DC due to AEs (UF-1, UF-2, extension) EEN vs. PBO: 10% vs. 7% Serious AEs (UF-1, UF-2) EEN vs. PBO: 3.3% vs. 4.1%; possibly related to treatment included HMB requiring transfusion (N=2), cholecystectomy (N=1) Common AEs (UF-1 and UF-2): hot flush, headache, fatigue, metrorrhagia Deaths: N=2, considered unrelated to treatment Bone loss with EEN: mean loss of BMD at lumbar spine at 6 mos -0.7% and at 12 mos -1.5%. Decline of >3% occurred in 27% of patients and decline >8% occurred in 1.7% of patients after 12 months. Thromboembolic events with EEN (UF-1, UF-2, extension) N=2

AE=adverse event

Drug and Alternatives	VANF Status	Other Considerations
Elagolix, estradiol, norethindrone (ORIAHNN)	TBD	Oral pill; twice daily Max duration 24 mos
Relugolix, estradiol, norethindrone (MYFEMBREE)	TBD	Oral pill; once daily Max duration 24 mos
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

Conclusions/Projected Place in Therapy

- EEN was more effective than placebo in reducing menstrual blood loss in premenopausal women with uterine leiomyoma. Effects appear to be sustained through 12 months of treatment. It is unclear how EEN compares to other GnRH agonists or antagonist since head-to-head study is lacking.
- The safety profile of EEN is notable for risk of bone loss, hot flushes, suicidal ideation and exacerbation of mood disorders, pregnancy loss, and the additional risks associated with estrogen and progestin. The addition of low dose estrogen plus progestin to elagolix appears to lessen the hypoestrogenic effects of elagolix alone. Treatment duration is limited to a maximum of 24 months due to concerns of bone loss.

References

1. Elagolix, estradiol, norethindrone (ORIAHNN) [online prescribing information]. Abbvie Inc. North Chicago, IL. June 2023.
2. FDA Clinical Review: ORIAHNN. Available at: 213388Orig1s000MultidisciplineR.pdf (fda.gov) . Accessed on February 13, 2024.
3. Schlaff WD, Ackerman RT, Al-Hendy A, et al. Elagolix for heavy menstrual bleeding in women with uterine fibroids. N Engl J Med. 2020;382:328-40.
4. Simon JA, Al-Hendy A, Archer DF, et al. Elagolix treatment for up to 12 months in women with heavy menstrual bleeding and uterine leiomyomas. Obstet Gynecol. 2020;135:1313-26.