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A REVIEW ON ELAGOLIX SODIUM: AN ORAL GONADOTROPIN - RELEASING HORMONE (GnRH) RECEPTOR ANTAGONIST FOR ENDOMETRIOSIS ASSOCIATED PAIN

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ABSTRACT

Elagolix sodium is an orally bioavailable, second-generation, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist. Is being developed AbbVie and Neurocrine Biosciences for the treatment of reproductive hormone-dependent disorders in women. Elagolix sodium is a drug used for the treatment of moderate to severe pain associated with endometriosis and the most common gynecological benign disease, uterine fibroids. Phase-I and phase-II clinical trials have demonstrated the safety of Elagolix sodium and its efficacy in partial and reversible suppression of ovarian estrogen production resulting in improvements in endometriosis-related pain. Phase-III clinical development for heavy menstrual bleeding associated with uterine fibroids in the previously mentioned locations. This drug is available and approved 150 mg once daily and 200 mg twice daily dosing regimens for the drug administration of moderate to severe pain associated with endometriosis. This review article summarizes the clinical pharmacology studies (i.e., mechanism of action, pharmacokinetics, and pharmacodynamics studies), pharmacogenomic activities, therapeutic trials, contraindications, adverse effects, ongoing clinical trials, safety and tolerability, and clinical trials of Elagolix sodium as an oral gonadotropin-releasing hormone (GnRH) receptor antagonist.

KEYWORDS: Elagolix sodium, GnRH Antagonist, Orilissa, Endometriosis, Uterine Fibroids.

INTRODUCTION

Elagolix sodium is a novel, non-peptide oral, short-acting competitive gonadotropin-releasing hormone (GnRH) receptor antagonist. For the management or treatment of moderate to severe pain associated with endometriosis, US FDA approved Elagolix tablets in July 2018. On the positive results in two replicate phase-III trials, this approval basis. Currently evaluating the additional phase-III trials of Elagolix as both monotherapy and in combination with low-dose hormone, add-back therapy in the same indication has occurred in the USA, Canada, and Puerto Rico countries.[14] And it is currently in development management of heavy menstrual bleeding associated with uterine fibroids.[1,2] Both endometriosis and uterine fibroids are estrogen-dependent conditions.[3] Elagolix sodium suppresses gonadotropin hormones and ovarian estrogen production in a dose-dependent manner, modulating circulating estrogen levels from partial suppression of estradiol (E2) at lower doses to nearly complete suppression at higher doses.[4]

Endometriosis

Endometriosis is enfeebling disease estimated to affect 10% of women of reproductive age, up to 50% of women with pelvic pain, and 20%-50% of women with reduced fertility.[6] Pelvic pain is the most common symptom, which presents as dysmenorrhea in over 98% of patients with symptomatic endometriosis and also non-menstrual pelvic pain. Pelvic pain varies greatly in intensity, frequency, and duration from patient to the patient associated with endometriosis. Non-menstrual pelvic pain or dyspareunia is generally chronic, hence lasts for more than six months, and it can be fitful throughout the menstrual cycle or continuous and may present as dull, throbbing, or sharp pain. In addition, the pain associated with endometriosis has been shown to weaken both work-related and non-work-related daily activities.[5,16,17,18] Fig. 1 shows the endometrial-like tissue growing outside of the uterus on another pelvic organ.

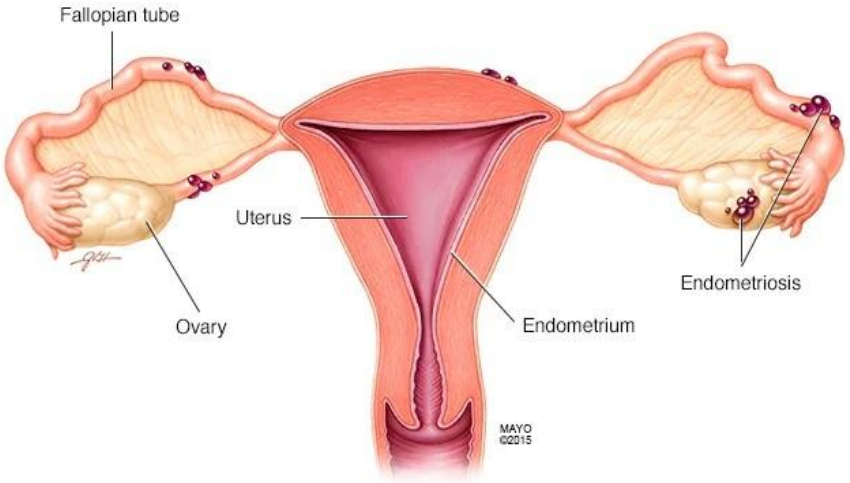

Fig. 1: In endometriosis, the bits of the uterine lining (Endometrium) grows outside of the uterus on other pelvic organs.

Pathogenesis: The specific pathogenesis of endometriosis is indistinct, and numerous scientists gave their speculations; however, out of them, just four hypotheses are famous and make sense of the pathogenesis to some degree. The four famous theories accept to explain the pathogenesis of endometriosis.[15,37]

1) **Retrograde menstruation:** First, this theory was proposed by Sampson during the 1920s. The hypothesis of retrograde menstruation is instinctively appealing and upheld by various lines of logical proof. Eutopic endometrium is sloughed via patent fallopian tubes into the peritoneal cavity during menstruation, according to this theory. Actually, the comprehensiveness of this phenomenon is supported by the finding of menstrual blood in the peritoneal fluid of up to 90% of healthy women with patent fallopian tubes going through laparoscopy during the peri-menstrual time of the cycle.[37]

2) **Benign metastasis:** The theory of benign metastasis proposes that ectopic endometrial implants are the result of lymphatic or hematogenous diffusion of endometrial cells.[38,39] Microvascular studies demonstrated the flow of lymph from the uterine body into the ovary, rendering possible a role for the lymphatic system in the etiology of ovarian endometriosis. In a baboon model of induced endometriosis and in 6-7% of women at lymphadenectomy documented the endometriosis.[40,41] The reports of histologically proven endometriotic lesions occurring in sites distant from the uterus, including bone, lung, and brain, are the strongest evidence of the theory of benign metastasis.[42]

3) **Impaired immunity:** Endometrial tissue begins to spill out of the uterine tube into the pelvic area as it stores the endometrial tissue. The white blood cells arrive in the pelvic area. They bind with the haptoglobin proteins found in patients with endometriosis and increment Interleukin creation. Different cytokines that move to the peritoneal fluid incorporate macrophage relocation inhibitory elements, TNF-alpha, IL-1beta, IL-6, and IL-8. The development elements of PGE2 cause adherence, growth, and inflammation. The white blood cells annihilate the endometrial layer rather than grow out of endometrial tissues present in the peritoneal layer, fallopian tube, and ovaries.[15]

4) **Hereditary and Stem cells:** A necessary correlate to theories proposing an endometrial origin to disease pathogenesis, hereditary or acquired properties of the endometrium, hereditary or acquired deformities of the peritoneal epithelium, and or defective immune clearance of sloughed endometrium are areas of active examination in the quest for the factor or factors that impact predisposition toward implantation of the displaced endometrial cells.[37] Within the endometrium, there are a lot of stem cells that are undifferentiated and can regrow inevitably, and they restore to form the endometrium layer. These stem cells come to the fallopian by retrograde menstruation, and because of the capacity to renew, they grow and form fibroids and ultimately reason endometrioses.[15]

Treatment: Including medical therapies and surgical interventions, most frequently, laparoscopic excision of endometriotic lesions is the current treatment option for the management of pain associated with endometriosis. The frequently used first-line therapy for endometriosis-associated pain is oral contraceptives. Gonadotropin-releasing hormone (GnRH) agonists are often considered, in the case of patients who don't have consistent symptom improvements, with oral contraceptives; or when oral contraceptives are contraindicated for safety reasons. In addition, endometriosis is a chronic, progressive disease. As a result, many patients will eventually require second-line therapy, including treatment with GnRH agonists. In reducing pelvic pain, even in patients who have become unresponsive to other therapies, GnRH agonists are effective but are associated with significant hypoestrogenic side effects, including unacceptable bone loss, which limits their long-term use.[19,20] Bone loss and vasomotor symptoms are reduced in hormone add-back therapy but prescribed in only one-third of women taking GnRH agonists.[21,22] In a dose-dependent manner, Elagolix sodium is an oral, short-acting, non-peptide, GnRH antagonist

demonstrated to suppress ovarian estrogen production.[23,24] 50 mg or 150 mg in healthy women for 42 days was associated with median estradiol values of 120 pg/mL, 53 pg/mL, and 30 pg/mL, respectively (data on file), daily administration of oral doses of placebo, or Elagolix. Dose selection in subsequent phase II studies, these phase-I data were informative. In women with endometriosis, phase-II studies included a 6-month, active comparator study (using leuprolide acetate), which evaluated the effects of various doses of Elagolix on bone mineral density (BMD) and estradiol levels in women with endometriosis conducted. These studies demonstrated that Elagolix 150 mg reduces endometriosis-associated pain, partially suppresses estradiol, and results in minimal changes in BMD.[25,26]

Uterine fibroids

Uterine fibroids are the most frequent gynecological benign disease, also known as uterine myomas or leiomyomas. The disease frequently develops without any signs or symptoms; hence establishing the actual predominance of this condition is complex. The prevalence of uterine fibroids reaches 70% of women, with an age-dependent increase in the incidence estimated by a recent epidemiological study.[7] The conditions associated with increased ovarian steroids exposure, such as early menarche, nulliparity, or first pregnancy delayed in late age, are included in other secondary risk factors. Despite the high prevalence, in only 15–30% of cases, uterine fibroids become symptomatic, sometimes seriously. Submucosal fibroids are more likely related to anemia and heavy menstrual bleeding (HMB), where the subserosal fibroids can cause compressive symptoms such as pain, dysuria, tenesmus, or constipation that is such symptoms linked to myomas and can depend on their localization in the uterus. By altering the endometrial cavity and its perfusion, reducing implantation, or by affecting endocrine and paracrine molecular mechanisms involved in embryonic development these ways uterine fibroids may also affect reproduction and fertility.[8,9]

Mechanism of action of elagolix sodium

Elagolix sodium is a highly potent (KD =54 pM) GnRH receptor antagonist. In the anterior pituitary gland**,** it inhibits endogenous GnRH signaling by binding competitively to GnRH receptors. The Mechanism of action (MoA) of the drug Elagolix sodium is different from long-acting GnRH receptor agonists, which induce 1–2 weeks of 'fare-up' by downregulating GnRH receptors. A benefit by allowing for rapid and reversible onset and offset provided by the competitive nature of Elagolix sodium competitive antagonism of the GnRH receptors, and hence more flexibility in modulating the hypothalamic-pituitary-gonadal axis. Fig. 2

shows an illustration that describes the Elagolix sodium mechanism of action (MoA) and downstream effects on gonadotropins and ovarian hormones.[1,10]

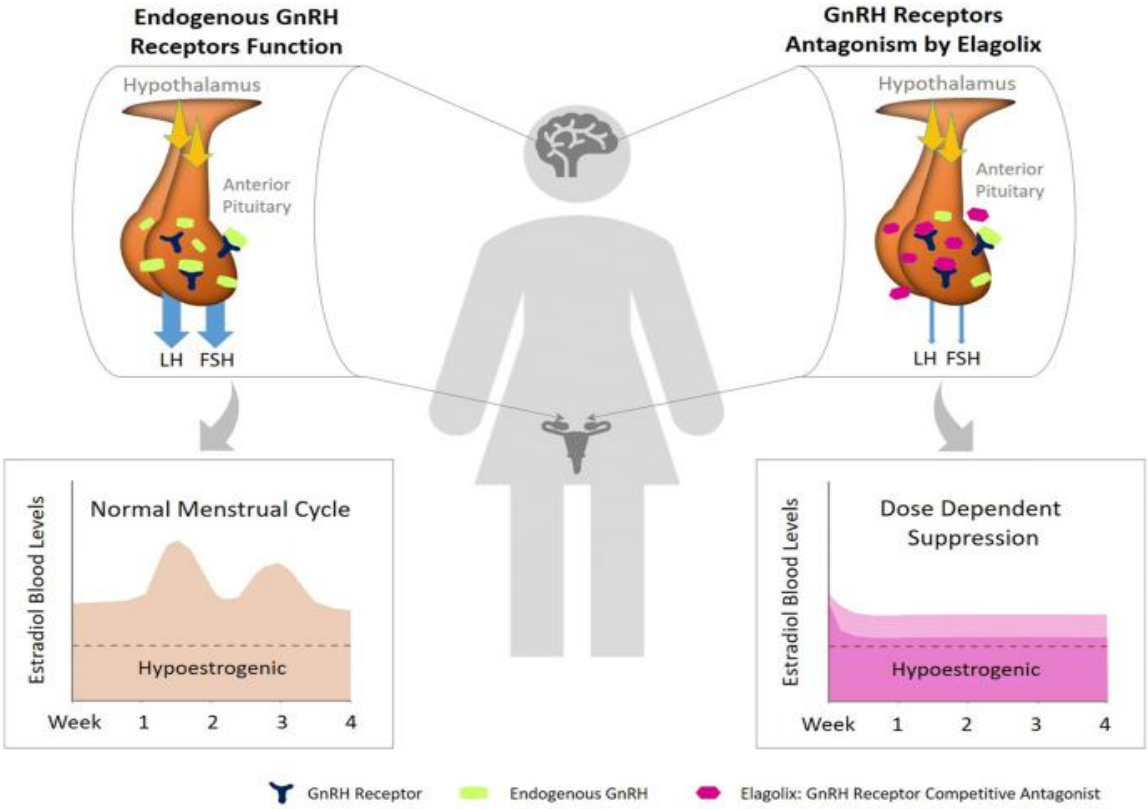

Fig. 2: Illustration of GnRH action and function during the normal female menstrual cycle, Elagolix sodium mechanism of GnRH receptors competitive antagonism at the anterior pituitary gland, and its downstream dose-dependent effects on circulating estradiol levels in the blood.

Pharmacokinetics of elagolix sodium

1) **Absorption:** Elagolix sodium is an orally bioavailable, non-peptide small molecule, amorphous solid. It is freely soluble in water. At either the 150 or 200 mg dose, Elagolix sodium is highly soluble per the Biopharmaceutics Classification System (BCS) throughout the physiological pH range. It exhibits high aqueous solubility (approximately 1 mg/mL), is a zwitterion with pKa 4.0 (acid) and 7.9 (base), and has an apparent low to moderate permeability (0.5–2.8×10−6 cm/s) based on in vitro Caco-2 studies. Elagolix sodium could classify as a BCS class III drug suggested by these data. Elagolix sodium drug contains one chiral center, and it is manufactured exclusively as the (R)-isomer. Orilissa™ (Elagolix) tablets for oral administration contain Elagolix sodium, the sodium salt of the active moiety Elagolix. Elagolix sodium is chemically known as sodium 4-

({(1R)-2-[5-(2-fluoro-3-methoxyphenyl)-3-{[2-fluoro-6- trifluoromethyl)phenyl]methyl}-4-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl]-1-phenylethyl}amino)butanoate.[1,4] The structure of Elagolix sodium is shown in Fig. 3.

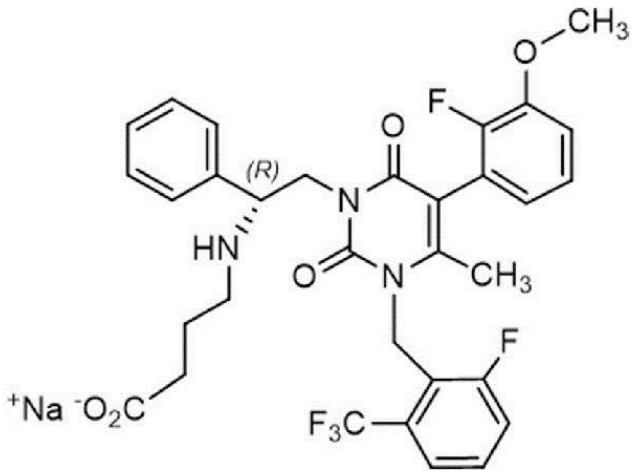

Fig. 3: Chemical Structure of Elagolix sodium. The chemical formula of Elagolix sodium is $C_{32}H_{29}F_5N_3NaO_5$. The Molecular weight of Elagolix sodium is 653.6, and the molecular weight of Elagolix free acid is 631.60.

Elagolix sodium absorption is rapid, with a time to maximum concentration (Tmax) of approximately one hour in a clinical pharmacokinetic study in healthy subjects. Elagolix sodium exposure (maximum concentration [Cmax] and area under the curve [AUC]) is dose-proportional from 100-400 mg twice daily and more than dose-proportional with single doses of 600–1200 mg.[1,4] Elagolix sodium has rapidly been absorbed through the gastrointestinal (GI) tract following oral administration, reaching its peak plasma concentrations in a dose-dependent manner within 30–60 min.[11] Elagolix 150 mg once-daily and 200 mg twice-daily PK parameters at a steady-state summarized in Table 1.

Table 1: Mean (% coefficient of variation) pharmacokinetic parameters at steady state of Elagolix sodium 150 mg QD or 200 mg BID.

Pharmacokinetic Parameters	150 mg qd	200mg bid
T_{max} (h^a)	1.0 (0.5-1.0)	1.0 (0.5–1.5)
C_{max} (ng/mL)	574 (29)	774 (68)
AUC_τ (ng × h/mL)	1292 (31)	1725 (57)
$T_{½}$ (h^b)	6.42±3.20	4.29±0.47
CL/F (L/h)	123 (21)	144 (43)
V_{ss}/F (L)	1674 (94)	881 (38)
R_{ac}	0.98 (7)	0.89 (19)
C_{max}/dose	3.83 (29)	3.87 (68)

AUC_{τ}/dose	8.61 (31)	8.62 (57)

Here,

AUC_{τ}: Area under the concentration–time curve during the dosing interval (τ) of 24 h for once-daily administration and 12 h for twice daily administration

bid: Twice daily

C_{max}: Maximum concentration

CL/F: Apparent clearance

qd: Once daily

R_{ac}: Accumulation Ratio

T_{max}: Time to maximum concentration

$t_{½}$: Terminal Elimination Half-Life

V_{ss}/F: Apparent volume of distribution at steady state

[a]: Data are reported as median (range)

[b]: Data are reported as harmonic mean±pseudo-standard deviation[2]

The absorption of Elagolix is rapid in clinical PK studies in healthy subjects, with a time to maximum concentration (Tmax) of approximately one hour. Elagolix exposure (maximum concentration [Cmax] and area under the curve [AUC]) is dose-proportional from 100 to 400 mg twice daily and more than dose-proportional with single doses of 600 to 1200 mg.[4] Various Elagolix formulations ranging from suspension to modified and immediate-release tablets are evaluated throughout the development program and acrosses multiple phase-I studies. The exposures did not vary significantly, consistent with a characteristic BCS III behavior, while variability in the PK profiles of Elagolix was observed across the tested formulations. For the endometriosis phase-III studies, as well as for the commercial formulation, an immediate-release tablet formulation was selected. For the phase-III tablet formulation, the final commercial tablet formulation of Elagolix is bioequivalent. The PK profiles of the phase-III and commercial 200 mg immediate-release tablet formulations are shown in Fig. 4.

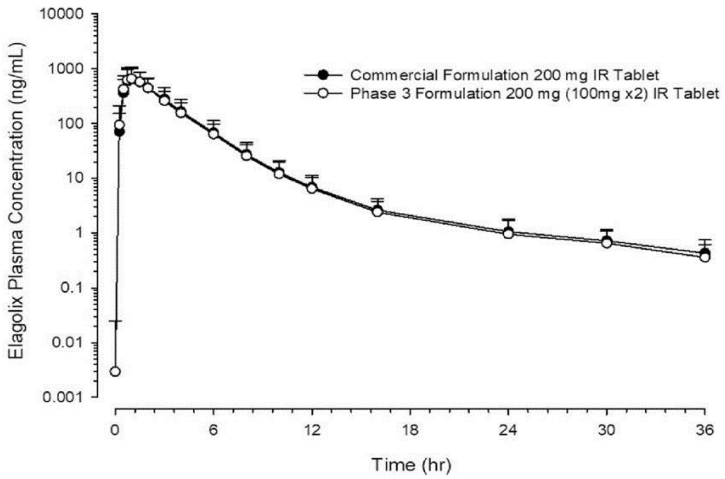

Fig. 4: Elagolix plasma concentration–time profiles of the phase-III and Commercial formulations of Orilissa™.

In Table-1, Elagolix 150 mg once-daily and 200 mg twice-daily PK parameters at a steady-state summarized. Dose proportional PK is demonstrated for both Elagolix dosages based on the dose-normalized Cmax and AUC values. Elagolix does not accumulate with repeated once daily or twice daily dosing.[1]

2) **Distribution:** Elagolix sodium is moderately (80%) bound to human plasma proteins and preferentially partitions into plasma instead of blood cellular components, with blood-to-plasma ratios of 0.6.[2] Using data from five-phase-I healthy volunteers and four-phase-III endometriosis patient studies based on population pharmacokinetic analyses, the Elagolix sodium estimated apparent central volume of distribution (Vc/F) was 257 L. Elagolix sodium is a medium of the hepatic uptake transporter organic anion transporting polypeptide (OATP) 1B1 based on in vitro studies, pharmacogenetics analysis of OATP1B1 variants, and clinical drug-drug interactions (DDIs) with single-dose rifampin. However, population PK analysis didn't identify the OATP1B1 genotype as a significant covariate on Elagolix Sodium Vc/F.[1,12]

3) **Metabolism:** Elagolix sodium metabolizes by multiple cytochrome P450 (CYP) enzymes in vitro, with predominant contribution from CYP3A4 (approximately 50%) and minor contributions from other CYPs.[13] Across a range of dosages, regimens vary from 2.4 to 6.3 h by plasma half-life of Elagolix sodium. The drug rapidly metabolized. Only 3% of the orally administered dose is excreted intact in the urine. The principal metabolite of Elagolix has been named NBI-61962. Which is unlikely to have any significant biologic effect due to its low plasma exposure and potency that is significantly less than Elagolix

(Ki value of 3.5 vs 0.9 nM).[11] Elagolix was the predominant form of radioactivity in plasma in a mass balance study in humans, following administrations of a single oral dose of 150 mg of [^{14}C] Elagolix to six healthy subjects. In the administered dose, 69% was recovered in feces and urine as metabolites, and a total of 11 minor metabolites were identified in plasma, each representing <3% of total plasma radioactivity. None of the metabolites in human plasma were classified as significant or disproportionate metabolites. A minor trace of an acyl-glucuronide metabolite in urine was detected in addition to CYP-mediated metabolites, suggesting a small contribution from uridine 5′-diphospho-glucuronosyltransferase (UGT) enzymes. Metabolite profiling of the feces (primary route of elimination, indicating biliary excretion) revealed that approximately 38% of the radioactive dose eliminate as the M1 metabolite, 26% was unchanged Elagolix, with the remainder being a combination of multiple minor metabolites. These data suggest that unchanged Elagolix is the significant drug-derived material in human plasma, and Elagolix is extensively metabolizing.[1]

4) **Elimination:** After reaching Cmax, the Elagolix concentration-time profile exhibits a biphasic characteristic, with an apparent terminal elimination half-life (t1/2) of approximately 4–6 h in healthy subjects.[4] Hence, repeated dosing of Elagolix once or twice daily does not result in significant drug accumulation in plasma. 90.1% of total radioactivity excretes in the feces, and urinary excretion accounted for only 2.9% of total radioactivity, with a mean whole recovery of 93% by approximately nine days after dosing observed in the mass balance single-dose study. With the population PK analysis, the minor urinary excretion of radioactivity was consistent, where the renal function was not associated with Elagolix PK parameters.[12] The OATP1B1 genotype was a statistically significant covariate on apparent clearance (CL/F). Hence, the minor change in CL/F (14%) is not considered clinically relevant when the poor and intermediate transporter genotypes are combined and compared with the extensive transporter genotype.[1,12] Fig. 5 shows the disposition and elimination mechanisms of Elagolix in humans.

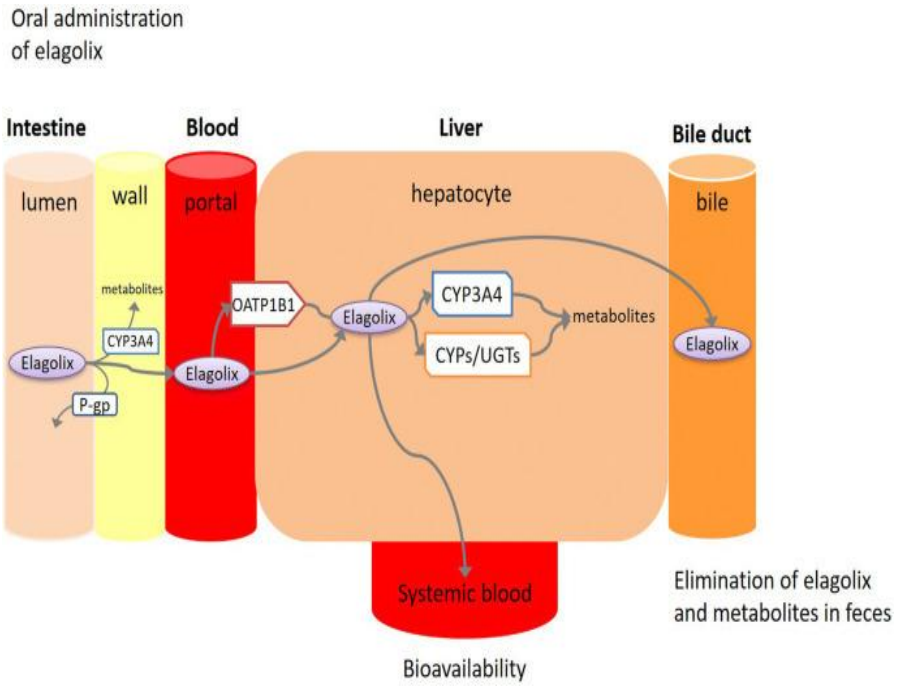

Fig. 5: The Disposition and Elimination mechanisms of Elagolix in humans.

Pharmacodynamics of elagolix sodium

Elagolix sodium is a highly potent (KD = 54 pM), non-peptide GnRH receptor antagonist. Elagolix binds competitively to GnRH receptors in the pituitary gland. Reduce estradiol and progesterone production because by blocking endogenous GnRH signaling, Elagolix suppresses luteinizing hormone (LH) and follicle-stimulating hormone (FSH).[2,24] When Elagolix sodium was administered orally at doses of 150 mg once daily or 100–400 mg twice daily in a clinical trial in healthy, premenopausal women, Elagolix rapidly suppressed LH, FSH, estradiol, and progesterone in a dose-dependent manner. In phase III trials, women with endometriosis are participating. To reduce concentrations of medium estradiol to ≈ 42 and 12 pg/ml, take Elagolix sodium 150 mg once daily and 200 mg twice daily regimens. Elagolix sodium 150 mg once daily and 200 mg twice daily regimens were associated with ovulation rates of ≈ 50 and 32% in healthy women administered Elagolix for three menstrual cycles. And transvaginal ultrasounds showed dose-dependent decreases in mean endometrial thickness relative to baseline.[14] Elagolix causes a rapid, dose-dependent suppression of pituitary gonadotropins, mainly luteinizing hormone (LH), and to a lesser extent, follicle-stimulating hormone (FSH), reaching its peak effects 4–6 hours after oral administration. Partial, dose-dependent suppression of ovarian estrogen production through inhibition of follicular development caused by the drug Elagolix. At the target dose of 150 mg once daily, Elagolix causes a partial suppression of estrogen production in most patients.[11]

Pharmacogenomics

To evaluate the impact of variants in the OATP1B1/SLCO1B1 gene on the subject's exposure to Elagolix was conducted by pharmacogenetic analysis. The SLCO1B1 genetic variant 521T>C genotype was assayed to classify subjects into one of three OATP1B1 transporter genotype statuses, i.e., extensive transporter (ET, homozygous wild-type 521T>C), intermediate transporter (IT, heterozygous for 521T>C), and intermediate transporter (PT, homozygous variant 521T>C). A total of 1314 DNA samples from four phase-III studies in subjects with moderate to severe endometriosis-related pain, and 462 DNA samples from 19 phase-I studies, were genotyped. 72% of subjects were extensive transporter (ET), 25% were intermediate transporter (IT), and 2.5% were intermediate transporter (PT), as suggested by the results. The disposition of Elagolix involves OATP1B1. And higher (less than twofold) plasma concentrations of Elagolix were observed in groups of patients and healthy subjects who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T>C). In most racial/ethnic groups, the frequency of this SLCO1B1 521 C/C genotype is generally<5%.[1,2,12]

Therapeutic trials

1) **Endometriosis:** For women with endometriosis and moderate to severe endometriosis-associated pain, Elagolix sodium 150 mg once daily and 200 mg twice daily enhanced dysmenorrhea symptoms and non-menstrual pelvic pain in the ELARIS EM-I and ELARIS EM-II trials. Compared with placebo recipients, significantly greater proportions of Elagolix sodium 150 mg once daily and 200 mg twice daily recipients had clinical responses for dysmenorrhea (46.4 and 75.8% vs. 19.6%; $p < 0.001$ for both comparisons). Non-menstrual pelvic pain (50.4 and 54.5% vs. 36.5%; $p < 0.001$ for both comparisons) at 3 months (primary endpoints) in ELARIS EM-I (Violet PETAL; NCT01620528).[3] Were sustained, the clinical response rates for dysmenorrhea and non-menstrual pelvic pain remained significantly higher with both Elagolix doses versus placebo at six months ($p \leq 0.008$ for all comparisons). Out of the 872 women randomized in ELARIS EM-I, 149 Elagolix sodium 150 mg once daily recipients and 138 Elagolix sodium 200 mg twice daily recipients entered the double-blind ELARIS EM-III extension study (NCT01760954). After an additional half-year of Elagolix therapy at the same dose in ELARIS EM-III (i.e., after 12 continuous treatment months), Elagolix 150 mg once daily and 200 mg twice daily recipients had response rates of 52.1 and 78.2%, respectively, for dysmenorrhea, 67.5 and 69.1% for non-menstrual pelvic pain, and 45.2 and 60.0% for

dyspareunia.[30] In Elagolix recipients the clinical response rates were significantly higher than placebo recipients with respect to dysmenorrhea (43.4 and 72.4% vs. 22.7%; $p < 0.001$ for both comparisons) and non-menstrual pelvic pain (49.8 and 57.8% vs. 36.5%; $p = 0.003$ and $p < 0.001$, respectively) at 3 months (primary endpoints) in ELARIS EM-II (Solstice; NCT01931670). At six months, these significant differences in clinical response rates maintain ($p \leq 0.01$ for all comparisons). At three months, both Elagolix doses significantly improved change from baseline in endometriosis-associated pain ($p < 0.001$ vs. placebo), and at both three months and six months, Elagolix 200 mg twice daily (but not 150 mg once daily) reduced the use of rescue analgesics relative to placebo ($p < 0.001$ vs. placebo). ELARIS EM-I and EM-II were randomized, double-blind, multicentre, Phase-III trials that registered 18–49 years aged premenopausal women with a surgical diagnosis of endometriosis within the previous ten years and moderate to severe endometriosis-associated pain [including a Composite Pelvic Signs and Symptoms Score (CPSSS) of Elagolix: First Global Approval 1505≥ 6 with scores of ≥ 2 for dysmenorrhea and non-menstrual pelvic pain at the screening].[3] Relative to placebo, Elagolix was related to significantly better reductions in dysmenorrhea ($p < 0.0001$), non-menstrual pelvic pain ($p = 0.0066$), and dyspareunia scores ($p = 0.007$) from baseline to week 8 (primary outcomes) in the multicentre, phase-II Daisy PETAL trial (NCT00973973). In this trial, 137 women have randomized to Elagolix sodium 150 mg once daily or placebo for an 8-week double-blind period and a following 16-week open-label period.[27] Elagolix significantly enhanced reduction from baseline in monthly mean pelvic pain relative to placebo in the randomized, double-blind, multinational, phase-II Tulip PETAL trial (NCT00797225). In this 24-week trial, women (n = 174) received Elagolix sodium 150 mg once daily, Elagolix sodium 250 mg once daily, and intramuscular monthly leuprorelin acetate or placebo; patients were assigned to leuprorelin or placebo were re-randomized to Elagolix at week 12.[32] In comparison with placebo, Elagolix sodium150 and 250 mg once daily did not significantly improve reductions in monthly mean endometriosis-associated pain from baseline to week 12 (primary efficacy measure) in the randomized, double-blind, multicentre, phase-II, Lilac PETAL trial (NCT00619866). Elagolix for 24 weeks or a placebo for 12 weeks received by participants (n = 155) with re-randomization to an Elagolix dose for the remaining 12 weeks.[29] Elagolix sodium 150 mg once daily and 75 mg twice daily were associated with a least-squares mean (LSM) changes in total CPSSS of −5.5 and −5.2 from baseline to week 24 in the randomized, double-blind, multicentre phase-II PETAL trial

(NCT00437658). While subcutaneous depot medroxyprogesterone acetate (injected at weeks 1 and 12) was associated with a LSM change of −5.3, the Women in PETAL received 24 weeks of double-blind treatment (n = 84 per treatment arm).[28]

2) **Uterine leiomyoma/ Uterine fibroids:** In uterine leiomyoma, heavy menstrual bleeding is a common problem; to reduce this heavy bleeding take Elagolix 300 mg tablet twice daily with a minimum dose of hormone add-back therapy in combination; and Significantly more Elagolix than placebo recipients achieved a clinical response at month 6 (68.5 vs. 8.7%; $p < 0.001$) in the randomized, double-blind, multicentre phase-III ELARIS UF-I trial (NCT02654054; M12-815).[33] Similarly, in a significantly higher proportion of patients than placebo (76.2 vs. 10.1% achieving clinical response at month 6; $p < 0.001$) in the randomized, double-blind, multicentre phase-III ELARIS UF-II trial (NCT02691494; M12-817). Clinical responses with Elagolix therapy were strong. With 87.9% of women achieving clinical response at month 12, Elagolix 300 mg twice daily in combination with low-dose hormone add-back therapy decreases heavy menstrual bleeding for up to 12 months in the randomized, double-blind, multicentre phase-III ELARIS UF-EXTEND extension study (NCT02925494; M12-816). In ELARIS UF-EXTEND, patients who had received Elagolix 300 mg twice daily with or without hormone add-back therapy in ELARIS UF-I orELARIS UF–II received an additional six months of the same treatment, and patients who had initially received a placebo were randomized to either of the two active treatment groups.[14] Considerably higher proportions of patients receiving Elagolix monotherapy clinical responses than patients receiving placebo (92, 85, and 79% vs. 27% at month 6; all $p < 0.001$ vs. placebo) in the randomized, double-blind, multinational phase-IIb (NCT01817530; M12-813) [cohort 1 results; n = 259] achieved by Elagolix in combination with low-dose hormone add-back therapy, and Elagolix in combination with standard-dose hormone add-back therapy.[34] Mean endometrial thickness decreased by 0.52, 1.33, and 0.56 mm from baseline to month 6 in the respective Elagolix groups while increasing by 2.1 mm with placebo (cohort 1; $p \leq 0.05$ for Elagolix plus low-dose hormone therapy vs. placebo).[35] Compared with the placebo group, Elagolix groups had a significantly better mean reduction in symptom severity and betterment in health-related quality of life from baseline to month 6 (cohort 1; $p \leq 0.001$ for all comparisons).[36] Efficacy results in cohort 2 were coherent with those in cohort 1. In each cohort, the patient assigns to Elagolix, Elagolix in combination with low- or standard-dose hormone add-back therapy or

placebo.[34,35,36] In cohort 1, Elagolix was administered at 300 mg twice daily and 600 mg once daily in cohort 2.[35] Elagolix considerably improves the mean percentage change in MBL from baseline to month three relative to placebo (reductions of 72–98% with Elagolix vs. diminutions of 8–41% with placebo; $p \leq 0.01$ for all doses vs. their respective placebo) in the randomized, dose-ranging, proof-of-concept phase-IIa study (NCT01441635; M12-663).[31] The highest mean percentage reduction was in women receiving Elagolix 300 mg twice daily (98% vs. 41% with placebo; $p \leq 0.001$). Patients received Elagolix 100, 200, or 300 mg twice daily, or Elagolix 400 mg once daily for 3 months (n = 33, 35, 30, and 32, respectively) in the placebo-controlled treatment groups.[31] The trials discussed in this section registered premenopausal women aged 18–51 years or 20–49 years with heavy menstrual bleeding associated with uterine fibroids.[31,33,36,] In the phase IIb trial and the replicate, phase III ELARIS UF-I and ELARIS UF-II trials, the main endpoint was the percentage of responders based on menstrual blood loss (MBL) volume reduction in the final month. And the clinical response was defined as MBL < 80 mL and ≥ 50% reduction from baseline, as measured using the alkaline hematin method.[14]

Contraindications

- Elagolix sodium not be given to pregnant women. It is given early in pregnancy and may increase the risk of early pregnancy loss.
- Women who have osteoporosis also have not to take Elagolix sodium because of the risk of further bone loss.
- The women with severe hepatic impairment because at the risk of bone loss.
- It contraindicates with the women who use the powerful organic anion transporting polypeptide (OATP) 1B1 inhibitors (e.g., cyclosporine and gemfibrozil).[2]

Adverse reactions

1) **Serious adverse events:** The most common serious adverse events reported for subjects treated with Elagolix sodium (Orilissa^{TM}) in the two placebo-controlled clinical trials (Studies EM-1 and EM-2) included appendicitis (0.3%), abdominal pain (0.2%), and back pain (0.2%).
2) **Common adverse reactions:** The common adverse reactions of Elagolix sodium (Orilissa^{TM}) 150 mg Once Daily and 200 mg Twice Daily are hot flush or night sweats,

headache, nausea, insomnia, mood alteration, mood swings, amenorrhea, depressed mood, depression, depressive symptoms and tearfulness, anxiety, arthralgia.

3) **Less common adverse reactions:** Decreased libido, diarrhea, abdominal pain, weight gain, dizziness, constipation, and irritability are the some less common adverse reactions shown in Study EM-1 and Study EM-2 adverse reactions reported in ≥ 3% and < 5% in either Elagolix sodium (Orilissa^{TM}) dose group and better than placebo.

The other adverse reactions are bone loss, suicidal ideation, suicidal behavior and exacerbation of mood disorders, hepatic transaminase elevations, changes in lipid parameters, hypersensitivity reactions, endometrial effects, and effects on the menstrual bleeding patterns.[1,2,14]

Ongoing clinical trials

In ongoing clinical trials, Elagolix sodium with or without hormone add-back therapy (estradiol/norethindrone acetate) evaluates. Recruitment is currently in progress for two randomized phases III trials. And both monotherapy and in combination with hormone add-back therapy in the management of moderate to severe endometriosis-associated pain in premenopausal women will be evaluated by Elagolix sodium. In the USA and Canada, the M16-383 dose increases trial (NCT03343067) enroll patients, while in the USA, Canada, and Puerto Rico, the placebo-controlled M14- 702 trial (NCT03213457) is enrolling. In the USA and Puerto Rico, a randomized, placebo-controlled phase IIIb trial (NCT03271489; M16-283) of Elagolix with or without estradiol/norethindrone acetate in the management of heavy menstrual bleeding associated with uterine fibroids in premenopausal women is currently recruiting participants. Phase III trials evaluating the ELARIS UF-I trial are underway at centers in the USA, Canada, and Puerto Rico. In the ELARIS UF-II trial in the USA and Canada, women who have to treat in ELARIS UF-I or UF–II have entered the ongoing extension study (ELARIS UF-EXTEND).[2,14]

Safety and Tolerability

In general, Elagolix has had an acceptable safety and tolerability profile. It is tolerating in clinical trials to date, and the incidences of overall side effects have been similar between Elagolix and placebo groups. Hot flushes (10.3%), nausea (7.4%), and headache (5.9%) are the most common side effects among Elagolix users (150 mg q.d.). Hot flushes (10.3%), nausea (7.4%), and headache (5.9%) are the most common side effects among Elagolix users (150 mg q.d.). Upon continued use for six months of Elagolix, the incidence of each of these

side effects increased to about 10%. Elagolix uses in the number of days with any vaginal bleeding from 23% at the screening to 14% after eight weeks. During the eight weeks, about 25% of patients on Elagolix (150 mg q.d.) developed amenorrhea, but this number decreased to 7.6% after 24 weeks. [27] Several pregnancies have to report in the Elagolix trials review of all the data from the early clinical development program of Elagolix to date estimates an annualized pregnancy rate of approximately 5% for the 150 mg q.d. dose.[28] The occurrence of these pregnancies explains by the fact that the degree of ovarian suppression with Elagolix is dose-dependent and not as profound as it is with other GnRH analogs, and plausibly the administered dose of Elagolix was not adequate to completely suppress ovarian function in these patients and therefore ovulation and subsequently, pregnancy followed. Two pregnancies have resulted in the delivery of healthy infants at term. One pregnancy resulted in a spontaneous miscarriage, and one resulted in the delivery of an infant with a tracheoesophageal fistula, with neither of these adverse outcomes assigned to Elagolix by the investigators, other pregnancy outcome was a cleft palate.[11,28] No teratogenic effects at all doses studied (30–98× the clinically relevant dosage) reveal in preclinical studies with Elagolix. An extensive review (e.g., timing of Elagolix exposure relative to organogenesis, absence of teratogenic findings in animal toxicological studies, and background incidence of this abnormality, among others) of congenital abnormality suggests that it is unlikely to be related to Elagolix; however, the right relationship remains unknown. Elagolix causes a small but significant reduction in BMD at the spine after 12 weeks and at the spine and femur after 24 weeks, about the effects on BMD. [28,29]

CONCLUSION

Elagolix sodium is an orally bioavailable, second-generation, non-peptide gonadotropin-releasing hormone (GnRH) receptor antagonist used to treat endometriosis. Elagolix sodium clinical pharmacology characteristics, the mechanism of action, pharmacokinetics and pharmacodynamics studies, and pharmacogenomic study in clinical studies in healthy subjects and women with endometriosis. The Mechanism of action (MoA) of Elagolix sodium is different from long-acting GnRH receptor agonists because, in the anterior pituitary gland**,** it inhibits endogenous GnRH signaling by binding competitively to GnRH receptors. Elagolix sodium is freely soluble in water; hence the absorption of Elagolix is rapid in clinical PK studies in healthy subjects, with a time to maximum concentration (Tmax) of approximately one hour. Linear PK over the efficacious dose range (150 mg once daily to 200 mg twice daily) and rapid PD onset and offset, leading to dose-dependent partial

suppression (150 mg once daily) and near-complete suppression (200 mg twice daily) of gonadotropin and ovarian hormones all are clinical pharmacology characteristics consists in Elagolix sodium. The bioavailability of Elagolix is not significantly impacted by food, has a manageable drug-drug interaction profile with most co-administered medications, and is inadvisable in women with severe hepatic impairment (Child-Pugh C). With the population PK analysis, the minor urinary excretion of radioactivity was consistent. Uterine fibroids (UFs) are the most common. Elagolix uses in uterine fibroids treatment (the most common gynecological benign disease) because, among other more efficient treatments, the gonadotropin-releasing hormone (GnRH) antagonist has a non-neutral safety profile. The pharmacogenomics analysis conducts to assess the impact of variants in the OATP1B1/SLCO1B1 gene on the subject's exposure to Elagolix. Generally, Elagolix sodium not be given to pregnant women because it may increase the risk of early pregnancy loss. It is one of the severe contraindications of Elagolix sodium. Night sweats, headache, nausea, insomnia, mood alteration, mood swings, amenorrhea, depressed mood, depression, depressive symptoms or tearfulness, anxiety, and arthralgia are the most common adverse effects of Elagolix. At the centers in the USA, Canada, and Puerto Rico, the Phase III clinical trials currently evaluating the ELARIS UF-I test are underway. Elagolix has a safety and tolerability profile; who has acceptable is well tolerated in clinical trials to date, and incidences of overall side effects have been similar between Elagolix and placebo groups. Generally, the complete characterization of the Elagolix clinical pharmacology profile studies and the model-based analyses played a crucial role in the approval of Elagolix as the first oral GnRH receptor antagonist for the treatment of moderate to severe pain associated with endometriosis and the uterine fibroids.

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Conflict of interest

The authors declare no conflict of interest.

Abbreviations

GnRH: Gonadotropin Releasing Hormone; US FDA: United State Food and Drug Administration; USA: United States of America; BMD: Bone Mass Density; HMB: Heavy Menstrual Bleeding; KD: Dissociation Constant; MoA: Mechanism of Action; BCS:

Biopharmaceutical Classification System; pKa: Acid Dissociation Constant; Caco: Cancer coli; pH: Potential of Hydrogen; Tmax: Time to reach maximum concentration; Cmax: Maximum Concentration; AUC: Area Under Curve; GIT: Gastro-Intestinal Tract; Pk: Pharmacokinetic; qd: Every Day/ Once a day; bid: Twice a day; CL/F: Apparent Clearance; Rac: Accumulation Ratio; $t_{1/2}$: Terminal Elimination Half Life; V_{ss}/F: Apparent Volume of Distribution at Steady State; OATP: Organic Anion Transporting Polypeptide; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; ET: Extensive Transport; IT: Intermediate Transport; EM: Endometriosis; UF: Uterine Fibroids; LSM: Least Square Means.

REFERENCES

1. Mohamad Shebley, Akshanth R. Polepally, Ahmed Nader, Juki W. Ng, Insa Winzenborg, Cheri E. Klein, Peter Noertersheuser, Megan A. Gibbs, Nael M. Mostafa. Clinical Pharmacology of Elagolix: An Oral Gonadotropin-Releasing Hormone Receptor Antagonist for Endometriosis. Clinical Pharmacokinetics, 2020; 59: 297–309.
2. Orilissa™ (elagolix) [United States package insert]. North Chicago, IL. AbbVie Inc, 2018.
3. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF. Treatment of endometriosis-associated pain with elagolix, an oral GnRH antagonist. N Engl J Med, 2017; 377(1): 28–40.
4. Ng J, Chwalisz K, Carter DC, Klein CE. Dose-dependent suppression of gonadotropins and ovarian hormones by elagolix in healthy premenopausal women. J Clin Endocrinol Metab, 2017; 102(5): 1683–91.
5. Bruce Carr, Linda Giudice, W. Paul Dmowski, Chris O'Brien, Ping Jiang, Joshua Burke, Roland Jimenez, Steven Hass, Mahesh Fuldeore, Kristof Chwalisz. Elagolix, an oral GnRH antagonist for endometriosis associated pain: a randomized controlled study. Journal of Endometriosis and Pelvic Pain Disorders, 2013; 5(3): 105-115.
6. Hoffman BL, Schorge JO, Schaffer JI. Endometriosis. Williams gynecology. 2nd ed. Chap. 10. New York: McGraw-Hill, 2008.
7. Stewart EA, Cookson CL, Gandolfo RA, Schulze-Rath R. Epidemiology of uterine fibroids: a systematic review. BJOG, 2017; 124(10): 1501–1512.
8. Bulun S. Uterine fibroids. N Engl J Med, 2013; 369(14):1344–1365.
9. Manuela Neri, Gian Benedetto Melis, Elena Giancane, Valerio Vallerino, Monica Pilloni, Bruno Piras, Alessandro Loddo, Anna Maria Paoletti, Valerio Mais. Clinical Utility of

Elagolix As An Oral Treatment For Women With Uterine Fibroids: A Short Report On The Emerging Efficacy Data. International Journal of Women's Health, 2019; 11: 535–546.

10. Dun EC, Taylor HS. Elagolix: a promising oral GnRH antagonist for endometriosis-associated pain. Oncotarget, 2017; 8(59): 99219–20.
11. Mohammad Ezzati1 & Bruce R Carr. Elagolix, a novel, orally bioavailable GnRH antagonist under investigation for the treatment of endometriosis-related pain, Womens Health, 2015; 11(1): 19–28.
12. Winzenborg I, Nader A, Polepally AR, Liu M, Degner J, Klein CE. Population pharmacokinetics of elagolix in healthy women and women with endometriosis. Clin Pharmacokinet, 2018; 57(10): 1295–306.
13. Ng J, Salem A, Carter D, Williams LA, Klein CE. Efect of the coadministration of ketoconazole on the pharmacokinetics and safety of elagolix in healthy premenopausal females. Clin Pharmacol Ther, 2016; 99: S55.
14. Yvette N. Lamb. Elagolix: First Global Approval. Drugs, 2018; 78: 1501–1508.
15. Joyson Paul, Rohit Bhatia. Elagolix Sodium: Novel GnRH Antagonist for the Treatment of Endometriosis. J Clin Anesthes Res, 2021; 2(1): 1-6.
16. Gao X, Yeh YC, Outley J, Simon J, Botteman M, Spalding J. Health-related quality of life burden of women with endometriosis: a literature review. Curr Med Res Opin, 2006; 22(9): 1787-1797.
17. Fourquet J, Báez L, Figueroa M, Iriarte RI, Flores I. Quantification of the impact of endometriosis symptoms on health related quality of life and work productivity. Fertil Steril, 2011; 96(1): 107-112.
18. Nnoaham KE, Hummelshoj L, Webster P. World Endometriosis Research Foundation Global Study of Women's Health Consortium. Impact of endometriosis on quality of life and work productivity: a multicenter study across ten countries. Fertil Steril, 2011; 96(2): 366, e8.
19. Batzer FR. GnRH analogs: options for endometriosis associated pain treatment. J Minim Invasive Gynecol, 2006; 13(6): 539-545.
20. Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. N Engl J Med, 2008; 359(11): 1136-1142.
21. Surrey ES. Gonadotropin-releasing hormone agonist and add-back therapy: what do the data show? Curr Opin Obstet Gynecol, 2010; 22(4): 283-288

22. Fuldeore MJ, Marx SE, Chwalisz K, Smeeding JE, Brook RA. Add-back therapy use and its impact on LA persistence in patients with endometriosis. Curr Med Res Opin, 2010; 26(3): 729-736.
23. Struthers RS, Xie Q, Sullivan SK. Pharmacological characterization of a novel nonpeptide antagonist of the human gonadotropin-releasing hormone receptor, NBI-42902. Endocrinology, 2007; 148(2): 857-867.
24. Struthers RS, Nicholls AJ, Grundy J. Suppression of gonadotropins and estradiol in premenopausal women by oral administration of the non-peptide gonadotropin-releasing hormone antagonist elagolix. J Clin Endocrinol Metab, 2009; 94(2): 545-551.
25. Imani R, Thai-Cuarto D, Jimenez R, Burke J, Kroll R, O'Brien C. Petal study: safety, tolerability and effectiveness of elagolix, an oral GnRH antagonist for endometriosis. Fertil Steril, 2009; 92(3): S111-S112.
26. Dlugi AM, Miller JD, Knittle J. Lupron Study Group. Lupron depot (leuprolide acetate for depot suspension) in the treatment of endometriosis: a randomized, placebo controlled, double-blind study. Fertil Steril, 1990; 54(3): 419-427.
27. Carr B, Giudice LC, Dmowski WP. Elagolix, an oral GnRH antagonist for endometriosis-associated pain: a randomized controlled study. J. Endometriosis Pelvic Pain Disorder, 2013; 5(3): 105–115.
28. Carr BR, Dmowski WP, O'Brien C. Elagolix, an oral GnRH antagonist versus subcutaneous depot medroxyprogesterone acetate for the treatment of endometriosis: effects on bone mineral density. Reprod. Sci, 2014; (11): 1341-51.
29. Diamond MP, Carr B, Dmowski WP. Elagolix treatment for endometriosis-associated pain: results from a phase 2, randomized, double-blind, placebo-controlled study. Reprod. Sci, 2014; 21(3): 363–371.
30. Surrey E, Taylor HS, Giudice L. Long-term outcomes of elagolix in women with endometriosis: results from two extension studies. Obstet Gynecol, 2018; 132(1): 147–60.
31. Archer DF, Stewart EA, Jain RI. Elagolix for the management of heavy menstrual bleeding associated with uterine fibroids: results from a phase 2a proof-of-concept study. Fertil Steril, 2017; 108(1): 152–60.e4.
32. Acs N, O'Brien C, Jiang P. Treatment of endometriosis associated pain with elagolix, an oral GnRH antagonist: results from a phase 2, randomized controlled study. J Endometriosis Pelvic Pain Disorder, 2015; 7(2): 56–62.

33. AbbVie, Neurocrine Biosciences Inc. AbbVie announces positive topline results from phase-3 study evaluating investigational elagolix in women with uterine fibroids [media release]. http:// www.abbvie.com. Accessed 21 Feb 2018.
34. Stewart E, Owens C, Duan WR. Elagolix alone and with add-back decreases heavy menstrual bleeding in women with uterine fibroids. Conference Abstract, 2017.
35. Simon JA, Stewart EA, Owens C. Elagolix treatment in women with heavy menstrual bleeding-associated with uterine fibroids: Efficacy and safety results from a phase 2b study. Fertil Steril, 2017; 108(3): e26–7.
36. Diamond M, Soliman AM, Gao J. Elagolix improves quality of life in women with heavy menstrual bleeding associated with uterine fibroids: evidence from a phase 2b randomized trial. Fertil Steril, 2017; 108(3): e27.
37. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. Fertil Steril, 2012; 98(3): 511- 519.
38. Halban J. Metastatic hysteroadenosis. Wien klin Wochenschr, 1924; 37: 1205–6.
39. Sampson JA. Metastatic or Embolic Endometriosis, due to the Menstrual Dissemination of Endometrial Tissue into the Venous Circulation. Am J Pathol, 1927; 3: 93–110 43.
40. Hey-Cunningham AJ, Fazleabas AT, Braundmeier AG, Markham R, Fraser IS, Berbic M. Endometrial stromal cells and immune cell populations within lymph nodes in a nonhuman primate model of endometriosis. Reprod Sci, 18: 747–54.
41. Javert CT. The spread of benign and malignant endometrium in the lymphatic system with a note on coexisting vascular involvement. Am J Obstet Gynecol, 1952; 64: 780–806.
42. Jubanyik KJ, Comite F. Extrapelvic endometriosis. Obstet Gynecol Clin North Am, 1997; 24: 411– 40.