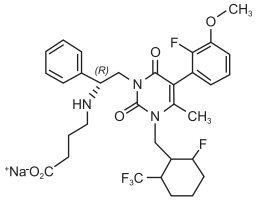
Getolix™
(Elagolix)

گیٹولِکس

Film-coated Tablets
150mg & 200mg

DESCRIPTION
Getolix (Elagolix) is a nonpeptide small molecule, Gonadotropin releasing hormone (GnRH) receptor antagonist. Elagolix sodium is chemically described 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. Its molecular formula is $C_{32}H_{29}F_5N_3O_5Na$ and the structural formula is:



Elagolix Sodium

QUALITATIVE AND QUANTITATIVE COMPOSITION
Getolix (Elagolix) Tablets are available for oral administration as:

Getolix Tablets 150mg
Each film-coated tablet contains:
Elagolix Sodium equivalent to Elagolix…150mg

Getolix Tablets 200mg
Each film-coated tablet contains:
Elagolix Sodium equivalent to Elagolix…200mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Elagolix is a GnRH receptor antagonist that inhibits endogenous GnRH signaling by binding competitively to GnRH receptors in the pituitary gland. Administration of Elagolix results in dose-dependent suppression of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to decreased blood concentrations of the ovarian sex hormones, estradiol and progesterone.

Pharmacokinetics
Absorption
In healthy premenopausal women, oral administration of Elagolix resulted in a rapid absorption with median time to maximum concentration in plasma (T_{max}) values of approximately 1 hour. The administration of Elagolix with a high-fat meal reduced the Elagolix area under the plasma concentration-time curve from time 0 to infinity (AUC_{inf}) by 24%, reduced the peak plasma concentration (C_{max}) by 36%, and delayed the time to C_{max} (T_{max}) from 1 to 2 hours compared to administration under fasted conditions which is not expected to impact efficacy. Elagolix may be administered with or without food.

Distribution
Elagolix is approximately 80% bound to human plasma proteins. The mean blood-to-plasma ratio was 0.6.

Metabolism
Elagolix is primarily metabolized by CYP3A with minor contributions from CYP2D6, CYP2C8, and uridine glucuronosyltransferases (UGTs). Unchanged Elagolix is the major drug-derived material in human plasma (>90%).

Elimination
The major route of elimination is by hepatic metabolism with 90% and <3% of the dose excreted in feces and urine, respectively. O-demethyl metabolite and unchanged Elagolix were the major components in the feces (37.6% and 26.3%, respectively). The terminal phase elimination half-life ($t_{½}$) is 4 to 6 hours.

Special Population
Pediatrics
The pharmacokinetics of Elagolix have not been investigated in women less than 18 years of age.

Geriatrics
The pharmacokinetics of Elagolix have not been investigated in women older than 65 years.

Patients with Hepatic impairment
Elagolix exposures (C_{max} and AUC) are similar between women with normal hepatic function and women with mild hepatic impairment. Elagolix exposures in women with moderate and severe hepatic impairment are approximately 3- and 7-fold, respectively, higher than exposures from women with normal hepatic function.

THERAPEUTIC INDICATIONS
Getolix (Elagolix) is indicated for the management of moderate to severe pain associated with endometriosis.

DOSAGE AND ADMINISTRATION
Important Administration Points
1. Women should use effective methods of contraception not containing estrogen while on treatment with Getolix (Elagolix).
2. Treatment with Getolix (Elagolix) should be initiated at the time of the menstrual flow to decrease the risk of an undiagnosed pregnancy. Pregnancy should be excluded before starting treatment with Getolix (Elagolix).
3. Because of the dose-dependent loss of bone mineral density (BMD) associated with Getolix (Elagolix) treatment, the use of Elagolix 200mg twice daily should be limited to 6 months duration.
4. Take Getolix (Elagolix) at approximately the same time each day, with or without food.
5. Use the lowest effective dose, taking into account the severity of symptoms and treatment objectives.
6. Clinical studies with Getolix (Elagolix) have been limited to a 12-month exposure to the drug and therefore the safety and efficacy of Getolix (Elagolix) beyond 12 months have not been established.

Recommended Dose
Recommended Dosage and Duration of Use

Dosing Regimen	Maximum Treatment Duration	Coexisting Condition
Initiate treatment with Getolix (Elagolix) 150mg once daily	24 months	None
Consider initiating treatment with Getolix (Elagolix) 200mg twice daily	6 months	Dyspareunia
Initiate treatment with Getolix (Elagolix) 150mg once daily. Use of 200mg twice daily is not recommended.	6 months	Moderate hepatic impairment (Child-Pugh Class B)

Special Population
Geriatrics (> 65 years of age)
Getolix (Elagolix) is not indicated in postmenopausal women and has not been studied in women over 65 years of age.

Pediatric
Safety and effectiveness of Getolix (Elagolix) in patients less than 18 years of age has not been established.

Patients with Hepatic Impairment
No dose adjustment of Getolix (Elagolix) is required in women with mild hepatic impairment (Child-Pugh A). Getolix (Elagolix) 150mg once daily is the recommended dose in women with moderate hepatic impairment (Child-Pugh B), with treatment duration limited to 6 months; the 200mg twice daily dose is not recommended. Getolix (Elagolix) is contraindicated in women with severe hepatic impairment (Child-Pugh C).

Patient With Renal Impairment
No dose adjustment of Getolix (Elagolix) is required in women with any degree of renal impairment or end-stage renal disease (including women on dialysis).

Missed Dose
If a woman misses a dose of Getolix (Elagolix) she should be instructed to take it as soon as she remembers as long as it is on the same day. She should then resume the regular dosing schedule.
- 150mg once a day: no more than 1 tablet each day should be taken.
- 200mg twice a day: no more than 2 tablets each day should be taken.

CONTRAINDICATIONS
Elagolix is contraindicated in women:
- with hypersensitivity to the active substance or to any of the excipients of the product.
- who are, suspected to be, or may become pregnant during the course of therapy.
- with undiagnosed vaginal bleeding.
- with known osteoporosis, due to the risk of further bone loss.

- with severe hepatic impairment (Child-Pugh C).
- taking organic anion transporting polypeptide (OATP)1B1 inhibitors (e.g., cyclosporine and gemfibrozil), due to the risks of increased Elagolix plasma concentrations.

ADVERSE REACTIONS

Following adverse reaction have been reported with the use of Elagolix:
Hot flush, headache, nausea, bone loss, change in menstrual bleeding pattern and reduced ability to recognize pregnancy, suicidal ideation, suicidal behavior, and exacerbation of mood disorders and hepatic transaminase elevations.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363."

PRECAUTIONS

Bone Loss

Elagolix causes a dose-dependent decrease in bone mineral density (BMD). BMD loss is greater with increasing duration of use and may not be completely reversible after stopping treatment. Elagolix is contraindicated in women with known osteoporosis. Consider assessment of BMD in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss. Limit the duration of use to reduce the extent of bone loss.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy

Women who take Elagolix may experience a reduction in the amount, intensity or duration of menstrual bleeding, which may reduce the ability to recognize the occurrence of a pregnancy in a timely manner. Perform pregnancy testing if pregnancy is suspected, and discontinue Elagolix if pregnancy is confirmed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders

Promptly evaluate patients with depressive symptoms to determine whether the risks of continued therapy outweigh the benefits. Patients with new or worsening depression, anxiety or other mood changes should be referred to a mental health professional, as appropriate. Advise patients to seek immediate medical attention for suicidal ideation and behavior. Reevaluate the benefits and risks of continuing Elagolix if such events occur.

Hepatic Transaminase Elevations

Use the lowest effective dose of Elagolix and instruct patients to promptly seek medical attention in case of symptoms or signs that may reflect liver injury, such as jaundice. Promptly evaluate patients with elevations in liver tests to determine whether the benefits of continued therapy outweigh the risks.

Interactions with Hormonal Contraceptives

Advise women to use effective non-hormonal contraceptives during treatment with Elagolix and for 28 days after discontinuing Elagolix.

- *Increase in Estrogen Exposure and Potential Associated Increased Risks When Elagolix 200mg Twice Daily is Taken with Combined Hormonal Contraceptives*
  Co-administration of a combined oral contraceptive (COC) (containing 20mcg ethinyl estradiol/0.1mg levonorgestrel) following administration of Elagolix 200mg twice daily for 14 days increases the plasma ethinyl estradiol concentration by 2.2-fold compared to this COC alone. Elagolix 200mg twice daily co-administered with a COC containing ethinyl estradiol may lead to increased risk of ethinyl estradiol-related adverse events including thromboembolic disorders and vascular events and is not recommended.

- *Potential for Reduced Efficacy of Progestin-Containing Hormonal Contraceptives*
  Co-administration of Elagolix 200mg twice daily and a COC containing 0.1mg levonorgestrel decreases the plasma concentrations of levonorgestrel by 27%, potentially affecting contraceptive efficacy.

- *Reduced Efficacy of Elagolix*
  Based on the mechanism of action of Elagolix, estrogen-containing contraceptives are expected to reduce the efficacy of Elagolix. The effect of progestin-only contraceptives on the efficacy of Elagolix is unknown.

Pregnancy

Use of Elagolix is contraindicated in pregnant women. Exposure to Elagolix early in pregnancy may increase the risk of early pregnancy loss. Discontinue Elagolix if pregnancy occurs during treatment.

Nursing Mother

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Elagolix and any potential adverse effects on the breastfed child from Elagolix.

DRUG INTERACTIONS

Potential for Elagolix to Affect Other Drugs

Elagolix is:

- A weak to moderate inducer of cytochrome P450 (CYP) 3A. Co-administration with Elagolix may decrease plasma concentrations of drugs that are substrates of CYP3A.
- A weak inhibitor of CYP2C19. Co-administration with Elagolix may increase plasma concentrations of drugs that are substrates of CYP2C19.
- An inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with Elagolix may increase plasma concentrations of drugs that are substrates of P-gp.

Effects of Elagolix on Other Drugs

Concomitant Drug Class: Drug Name	Effect on Plasma Exposure of Concomitant Drug	Clinical Recommendations
Cardiac glycosides: digoxin	↑ digoxin	Increase monitoring of digoxin concentrations and potential signs and symptoms of clinical toxicity when initiating Elagolix in patients who are taking digoxin. If Elagolix is discontinued, increase monitoring of digoxin concentrations.
Benzodiazepines: oral midazolam	↓ midazolam	Consider increasing the dose of midazolam by no more than 2-fold and individualize midazolam therapy based on the patient's response.
Statins: rosuvastatin	↓ rosuvastatin	Monitor lipid levels and adjust the dose of rosuvastatin, if necessary.
Proton pump inhibitors: omeprazole	↑ omeprazole	No dose adjustment needed for omeprazole 40 mg once daily when co-administered with Elagolix. When Elagolix is used concomitantly with higher doses of omeprazole, consider dosage reduction of omeprazole.
Combined hormonal contraceptives: oral ethinyl estradiol/levonorgestrel	↑ethinyl estradiol ↓levonorgestrel	Advise women to use effective non-hormonal contraception during treatment with Elagolix and for 28 days after discontinuing Elagolix.

Potential for Other Drugs to Affect Elagolix

- Elagolix is a substrate of CYP3A, P-gp, and OATP1B1.
- Concomitant use of Elagolix 200mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of Elagolix 150mg once daily and strong CYP3A inhibitors to 6 months.
- Co-administration of Elagolix with strong CYP3A inducers may decrease Elagolix plasma concentrations and may result in a decrease of the therapeutic effects of Elagolix.
- Concomitant use of Elagolix 200mg twice daily and rifampin is not recommended. Limit concomitant use of Elagolix 150mg once daily and rifampin to 6 months.
- The effect of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of Elagolix is unknown. OATP1B1 inhibitors that are known or expected to significantly increase Elagolix plasma concentrations are contraindicated due to increased risk of Elagolix associated adverse reactions.

OVERDOSAGE

In case of overdose, monitor the patient for any signs or symptoms of adverse reactions and initiate appropriate symptomatic treatment as needed.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Getolix (Elagolix) Tablets 150mg are available in pack of 14's.
Getolix (Elagolix) Tablets 200mg are available in pack of 14's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

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Manufactured by:

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