SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eladiol 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Eladiol 200 mg film-coated tablets
Each tablet contains: Elagolix as Elagolix Sodium … 200mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eladiol 200 mg film-coated tablets
Beige colored, oblong shape, coated tablet one side engraved NQ and other side is plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Limitations of Use:
Limit the duration of use based on the dose and coexisting condition.

4.2 Posology and method of administration

Important Dosing Information

- Exclude pregnancy before starting ELADIOL or start ELADIOL within 7 days from the onset of menses.
- Take ELADIOL at approximately the same time each day, with or without food.
- Use the lowest effective dose, taking into account the severity of symptoms and treatment objectives.
- Limit the duration of use because of bone loss.

Table 1. Recommended Dosage and Duration of Use

Dosing Regimen	**Maximum Treatment**	**Coexisting Condition**
	Duration	
Initiate treatment with ELADIOL 150 mg once daily	24 months	None

Consider initiating treatment with ELADIOL 200 mg twice daily	6 months	Dyspareunia
Initiate treatment with ELADIOL 150 mg once daily. Use of 200 mg twice daily is not recommended.	6 months	Moderate hepatic impairment (Child-Pugh Class B)

Hepatic Impairment

- No dosage adjustment of ELADIOL is required in women with mild hepatic impairment (ChildPugh A).
- ELADIOL 150 mg once daily is recommended for women with moderate hepatic impairment (Child-Pugh B) with the duration of treatment limited to 6 months. Use of ELADIOL 200 mg twice daily is not recommended for women with moderate hepatic impairment.
- ELADIOL is contraindicated in women with severe hepatic impairment (ChildPugh C).

Missed Dose

- Instruct the patient to take a missed dose of ELADIOL on the same day as soon as she remembers and then resume the regular dosing schedule.
- 150 mg once daily: take no more than 1 tablet each day.
- 200 mg twice daily: take no more than 2 tablets each day.

4.3 Contraindications

ELADIOL is contraindicated in women:

- Who are pregnant. Exposure to ELADIOL early in pregnancy may increase the risk of early pregnancy loss.
- With known osteoporosis because of the risk of further bone loss.
- With severe hepatic impairment.
- Taking inhibitors of organic anion transporting polypeptide (OATP)1B1 (a hepatic uptake transporter) that are known or expected to significantly increase elagolix plasma concentrations.
- With known hypersensitivity reaction to ELADIOL or any of its inactive components.
- Reactions have included anaphylaxis and angioedema.

4.4 Special warnings and precautions for use

Bone Loss

ELADIOL 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. The impact of these BMD decreases on long-term bone health and future fracture risk are unknown. ELADIOL 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. Although the effect of supplementation with calcium and vitamin D was not studied, such supplementation may be beneficial for all patients.

Change in Menstrual Bleeding Pattern and Reduced Ability to Recognize Pregnancy Women who take ELADIOL 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 ELADIOL if pregnancy is confirmed.

Suicidal Ideation, Suicidal Behavior, and Exacerbation of Mood Disorders
Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with ELADIOL in the endometriosis clinical trials. ELADIOL subjects had a higher incidence of depression and mood changes compared to placebo, and ELADIOL subjects with a history of suicidality or depression had a higher incidence of depression compared to subjects without such a history. 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 ELADIOL if such events occur.

Hepatic Transaminase Elevations
In clinical trials, dose-dependent elevations of serum alanine aminotransferase (ALT) at least 3times the upper limit of the reference range occurred with ELADIOL. Use the lowest effective dose of ELADIOL 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 ELADIOL and for 28 days after discontinuing ELADIOL.
Increase in Estrogen Exposure and Potential Associated Increased Risks When ELADIOL 200 mg Twice Daily is Taken with Combined Hormonal Contraceptives
Co-administration of a combined oral contraceptive (COC) (containing 20 mcg ethinyl estradiol/0.1 mg levonorgestrel) following administration of ELADIOL 200 mg twice daily for 14 days increases the plasma ethinyl estradiol concentration by 2.2-fold compared to this COC alone. ELADIOL 200 mg 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 ELADIOL 200 mg twice daily and a COC containing 0.1 mg levonorgestrel decreases the plasma concentrations of levonorgestrel by 27%, potentially affecting contraceptive efficacy. Co-administration of

ELADIOL with COCs containing norethindrone acetate did not show reduction in plasma concentrations of norethindrone. Co-administration of ELADIOL with progestin-containing intrauterine contraceptive systems has not been studied.
Reduced efficacy of ELADIOL
Based on the mechanism of action of ELADIOL, estrogen-containing contraceptives are expected to reduce the efficacy of ELADIOL. The effect of progestin-only contraceptives on the efficacy of ELADIOL is unknown.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for ELADIOL to Affect Other Drugs Elagolix is:

- A weak to moderate inducer of cytochrome P450 (CYP) 3A. Co-administration with ELADIOL may decrease plasma concentrations of drugs that are substrates of CYP3A.
- A weak inhibitor of CYP 2C19. Co-administration with ELADIOL may increase plasma concentrations of drugs that are substrates of CYP2C19.
- An inhibitor of efflux transporter P-glycoprotein (P-gp). Co-administration with ELADIOL may increase plasma concentrations of drugs that are substrates of P-gp.

The effects of co-administration of ELADIOL on concentrations of concomitant drugs and the clinical recommendations for these drug interactions are summarized in Table 7.

Table 7. Drug Interactions: Effects of ELADIOL 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 ELADIOL in patients who are taking digoxin. If ELADIOL 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 ELADIOL. When ELADIOL 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 ELADIOL and for 28 days after discontinuing ELADIOL.

Potential for Other Drugs to Affect ELADIOL
Elagolix is a substrate of CYP3A, P-gp, and OATP1B1.
Concomitant use of ELADIOL 200 mg twice daily and strong CYP3A inhibitors for more than 1 month is not recommended. Limit concomitant use of ELADIOL 150 mg once daily and strong CYP3A inhibitors to 6 months.
Co-administration of ELADIOL with strong CYP3A inducers may decrease elagolix plasma concentrations and may result in a decrease of the therapeutic effects of ELADIOL. Concomitant use of ELADIOL 200 mg twice daily and rifampin is not recommended. Limit concomitant use of ELADIOL 150 mg once daily and rifampin to 6 months.
The effect of concomitant use of P-gp inhibitors or inducers on the pharmacokinetics of ELADIOL 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Use of ELADIOL is contraindicated in pregnant women. Exposure to ELADIOL early in pregnancy may increase the risk of early pregnancy loss. Discontinue ELADIOL if pregnancy occurs during treatment.
The limited human data with the use of ELADIOL in pregnant women are insufficient to determine whether there is a risk for major birth defects or miscarriage. Although two cases of congenital malformations were reported in clinical trials with ELADIOL, no pattern was identified and miscarriages were reported at a similar incidence across treatment groups.

Breast-feeding
No data in humans are available on excretion of Elagolix into milk. Available toxicological data in animals have shown excretion of Elagolix in milk. A risk to the newborns/infants cannot be excluded. Eladiol should not be used during breast-feeding.

Fertility
Based on the mechanism of action, there is a risk of early pregnancy loss if ELADIOL is administered to a pregnant woman.

Pregnancy Testing
ELADIOL may delay the ability to recognize the occurrence of a pregnancy because it may reduce the intensity, duration, and amount of menstrual bleeding. Exclude pregnancy before initiating treatment with ELADIOL. Perform pregnancy testing if pregnancy is suspected during treatment with ELADIOL and discontinue treatment if pregnancy is confirmed.

Contraception
Advise women to use effective non-hormonal contraception during treatment with ELADIOL and for 28 days after discontinuing ELADIOL.

4.7 Effects on ability to drive and use machines

Eladiol has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies conducted in mice (50, 150, or 500 mg/kg/day) and rats (150, 300, or 800 mg/kg/day) that administered elagolix by the dietary route revealed no increase in tumors in mice at up to 19-fold the MRHD based on AUC. In the rat, there was an increase in thyroid (male and female) and liver (males only) tumors at the high dose (12 to 13 fold the MRHD). The rat tumors were likely species-specific and of negligible relevance to humans. Elagolix was not genotoxic or mutagenic in a battery of tests, including the *in vitro* bacterial reverse mutation assay, the *in vitro* mammalian cell forward mutation assay at the thymidine kinase (TK+/-) locus in L5178Y mouse lymphoma cells, and the *in vivo* mouse micronucleus assay.
In a fertility study conducted in the rat, there was no effect of elagolix on fertility at any dose (50, 150, or 300 mg/kg/day). Based on AUC, the exposure multiple for the MRHD in women compared to the highest dose of 300 mg/kg/day in female rats is approximately 5-fold. However, because elagolix has low affinity for the GnRH receptor in the rat, and because effects on fertility are most likely to be mediated via the GnRH receptor, these data have low relevance to humans.

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Effect on Ovulation and Estradiol

In a 3-menstrual cycle study in healthy women, ELADIOL 150 mg once daily and 200 mg twice daily resulted in an ovulation rate of approximately 50% and 32%, respectively. In the Phase 3 trials in women with endometriosis, ELADIOL caused a dose-dependent reduction in median estradiol concentrations to approximately 42 pg/mL for 150 mg once daily regimen and 12 pg/mL for the 200 mg twice daily regimen.

Cardiac Electrophysiology

The effect of elagolix on the QTc interval was evaluated in a randomized, placebo- and positive- controlled, open-label, single-dose, crossover thorough QTc study in 48 healthy adult premenopausal women. Elagolix concentrations in subjects given a single dose of 1200 mg was 17-times higher than the concentration in subjects given elagolix 200 mg twice daily. There was no clinically relevant prolongation of the QTc interval.

Pharmacokinetics

The pharmacokinetic properties of ELADIOL in healthy subjects are summarized in Table 8. The steady state pharmacokinetic parameters under fasting conditions are summarized in Table 9.

Table 8. Pharmacokinetic Properties of ELADIOL in Healthy Subjects

Absorption		
T_{max} (h)		1.0
Effect of high-fat meal (relative to fasting)		AUC: ↓24%, Cmax: ↓36%
Distribution		
% Bound to human plasma proteins		80
Blood-to-plasma ratio		0.6
Metabolism		
Metabolism		CYP3A (major) Minor pathways include: CYP2D6, CYP2C8, and uridine glucuronosyl transferases (UGTs)
Elimination		
Major route of elimination		Hepatic metabolism
Terminal phase elimination half-life ($t_{1/2}$) (h)		4-6
% of dose excreted in urine		<3

% of dose excreted in feces		90

Table 9. Mean (%CV) Steady State Pharmacokinetic Parameters of ELADIOL

Pharmacokinetic Parameter (Units)	**150 mg Once Daily N = 6**	**200 mg Twice Daily N = 7**
C_{max} (ng/mL)	574 (29)	774 (68)
AUC_{τ} (ng•hr/mL)	1292 (31)	1725 (57)
CL/F (L/hr)	123 (21)	144 (43)
Vdss/F	1674 (94)	881 (38)
Rac	0.98 (7)	0.89 (19)

CV: Coefficient of variation
C_{max}: peak concentration
AUC_{τ}: area under the plasma concentration-time curve during the dosing interval (τ) i.e., 12 hours for twice daily regimen, 24 hours for once daily regimen.
CL/F: oral clearance
V_{dss}/F: apparent volume of distribution at steady state R_{ac}: drug accumulation ratio

Specific Populations

Patients with Renal Impairment
Elagolix exposures (C_{max} and AUC) are not altered by renal impairment. The mean exposures are similar for women with moderate to severe or end stage renal disease (including women on dialysis) compared to women with normal renal function.

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-fold and 7-fold, respectively, higher than exposures from women with normal hepatic function.

Racial or Ethnic Groups
No clinically meaningful difference in the pharmacokinetics of ELADIOL between White and Black subjects or between Hispanics and others was

observed. There is no clinically meaningful difference in the pharmacokinetics of ELADIOL between Japanese and Han Chinese subjects.

Body weight/Body mass index
Body weight or body mass index does not affect the pharmacokinetics of ELADIOL.

Drug Interaction Studies
Drug interaction studies were performed with ELADIOL and other drugs that are likely to be coadministered and with drugs commonly used as probes for pharmacokinetic interactions. Tables 10 and 11 summarize the pharmacokinetic effects when elagolix was co-administered with these drugs.

Table 10. Drug Interactions: Change in Pharmacokinetics of Elagolix in the Presence of Co-Administered Drugs

Co-administered Drug	**Regimen of Co-administered Drug**	**Regimen of Elagolix**	**N**	**Ratio (90% CI)***	
				C_{max}	**AUC**
Ketoconazole	400 mg once daily	150 mg single dose	11	1.77 (1.48 – 2.12)	2.20 (1.98 – 2.44)
Rifampin#	600 mg single dose	150 mg single dose	12	4.37 (3.62 – 5.28)	5.58 (4.88 – 6.37)
	600 mg once daily			2.00 (1.66 – 2.41)	1.65 (1.45 – 1.89)

CI: Confidence interval
*ratios for C_{max} and AUC compare co-administration of the medication with elagolix vs. administration of elagolix alone.
A single dose of 600 mg rifampin inhibits OATP1B1; 600 mg once daily dose of rifampin inhibits OATP1B1 and induces CYP3A.

No clinically significant changes in elagolix exposures were observed when coadministered with rosuvastatin (20 mg once daily), sertraline (25 mg once daily) or fluconazole (200 mg single dose).

Pharmacogenomics
Hepatic uptake of elagolix involves the OATP 1B1 transporter protein. Higher plasma concentrations of elagolix have been observed in patients who have two reduced function alleles of the gene that encodes OATP 1B1 (SLCO1B1 521T>C) (these patients are likely to have reduced hepatic uptake of elagolix and thus, higher plasma elagolix concentrations). The frequency of this SLCO1B1 521 C/C genotype is generally less than 5% in most racial/ethnic groups. Subjects with this genotype are expected to have a 78% mean increase in elagolix concentrations compared to subjects with normal

transporter function (i.e., SLCO1B1 521T/T genotype). Adverse effects of elagolix have not been fully evaluated in subjects who have two reduced function alleles of the gene that encodes OATP1B1 (SLCO1B1 521T>C).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol
Pregeletinized Starch
Povidone K-30
De-ionized Water
Sodium Carbonate Monohydrate
Magnesium Stearate

Tablet coating
Instamoist shield Aqua II
Ferric Oxide Red
Isopropyl Alcohol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Aluminium unit dose blisters.
Pack sizes of 14s, 28s & 56s film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Nabiqasim Industries Pvt. Ltd.
5th Floor, Commerce center, Hasrat Mohani Road, Karachi-74200, Pakistan

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