For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

REGESTRONE LX

1. Generic Name

Relugolix, Estradiol and Norethindrone Acetate Tablets (40 mg + 1 mg + 0.5 mg)

2. Qualitative and quantitative Composition:

Each film coated tablet contains:

Relugolix ……...40 mg

Estradiol Hemihydrate I.P.

Equivalent to Anhydrous Estradiol……1 mg

Norethindrone Acetate U.S.P.…….0.5 mg

Excipients…….……...q.s.

Colours: Ferric Oxide Yellow USP-NF & Titanium Dioxide I.P.

The list of excipients used are Lactose, Starch, Crospovidone, Sodium Lauryl sulphate, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxypropyl Methylcellulose, Polyethylene Glycol, Titanium Dioxide, Talcum powder and Ferric oxide Yellow.

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: 40 mg + 1 mg + 0.5 mg

4. Clinical particulars

4.1. Therapeutic indication

Indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women.

4.2. Posology and method of administration

Posology:

The recommended dose is 1 tablet once daily or as directed by the Physician.

Method of administration:

For oral use.

4.3. Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients.
- Venous thromboembolic disorder, past or present (e.g. deep venous thrombosis, pulmonary embolism).
- Arterial thromboembolic cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease).
- Known thrombophilic disorders (e.g. protein C, protein S or antithrombin deficiency or activated protein C (APC)-resistance, including Factor V Leiden
- Known osteoporosis.
- Headaches with focal neurological symptoms or migraine headaches with aura.

- Known or suspected sex-steroid influenced malignancies (e.g. of the genital organs or the breasts).
- Presence or history of liver tumours (benign or malignant).
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Pregnancy or suspected pregnancy and breastfeeding.
- Genital bleeding of unknown aetiology.
- Concomitant use of hormonal contraceptives.

4.4. Special warnings and precautions for use

Relugolix Estradiol & Norethisterone must only be prescribed after careful diagnosis.

Medical examination/consultation

Prior to the initiation or reinstitution of Relugolix Estradiol & Norethisterone, a complete medical history (including family history) must be taken. Blood pressure must be measured, and a physical examination must be performed guided by the contraindications. During treatment, periodic check-ups must be carried out according to standard clinical practice. Any hormonal contraception needs to be stopped prior to initiation of Relugolix Estradiol & Norethisterone.

Nonhormonal methods of contraception must be used for at least 1 month after initiation of treatment. Pregnancy must be ruled out prior to administering or re-initiation of Relugolix Estradiol & Norethisterone.

Risk of thromboembolic disorders

The use of medicinal products containing an estrogen and a progestogen increases the risk of arterial or venous thromboembolism (ATE or VTE) compared with no use. The risk of ATE/VTE with Relugolix Estradiol & Norethisterone has not been established. Relugolix Estradiol & Norethisterone contains doses of estrogen and progestogen lower than the doses used in combined hormonal contraceptives and are provided in combination with relugolix, a gonadotropin-releasing hormone (GnRH) receptor antagonist that suppresses ovarian production of estrogen and progesterone. Estradiol levels with Relugolix Estradiol & Norethisterone are in the range observed in the early follicular phase of the menstrual cycle. If an ATE/VTE occurs, treatment must be discontinued immediately. Relugolix Estradiol & Norethisterone is contraindicated in women with past or present venous or arterial thromboembolic disease.

Risk factors for venous thromboembolism (VTE)

The risk for venous thromboembolic complications in women using a product with an estrogen and progestogen may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors.

Table. Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index [BMI] over 30 kg/m^2)	Risk increases substantially as BMI rises.
Prolonged immobilisation, major surgery ormajor trauma	In these situations, it is advisable to discontinue use of the medicinal product (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after completeremobilisation.

Risk factor	Comment
Positive family history (VTE) ever in a sibling or parent especially at a relatively early age e.g.before 50 years.	If a hereditary predisposition is suspected, thewoman must be referred to a specialist for advice before using the medicinal product.
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age	Particularly above 35 years.

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered.

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

In the event of symptoms, women must be advised to get urgent medical attention and to inform the physician that she is taking Relugolix Estradiol & Norethisterone.

Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot or along a vein in the leg.
- pain or tenderness in the leg which may be felt only when standing or walking.
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:

- sudden onset of unexplained shortness of breath or rapid breathing.
- sudden coughing which may be associated with haemoptysis.
- sharp chest pain.
- severe light headedness or dizziness.
- rapid or irregular heartbeat. Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Risk factors for arterial thromboembolism (ATE)

Epidemiological studies have associated the use of estrogen/progestogen products with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, stroke). Arterial thromboembolic events may be fatal. The risk for arterial thromboembolic complications in women using a product with an estrogen and progestogen may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors.

Table. Risk factors for ATE

Risk factor	Comment
Increasing age	Particularly above 35 years.
Smoking	Women are to be advised not to smoke if theywish to use the medicinal product.
Hypertension	
Obesity (body mass index [BMI] over 30 kg/m^2)	Risk increases substantially as BMI increases.
Positive family history (ATE) ever in a siblingor parent especially at relatively early age e.g. before 50 years.	If a hereditary predisposition is suspected, thewoman must be referred to a specialist for advice before using the medicinal product.

Risk factor	Comment
Migraine	An increase in frequency or severity of migraine during use of the medicinal product (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms, women must be advised to get urgent medical attention and to inform the physician that she is taking Relugolix Estradiol & Norethisterone.

Symptoms of a cerebrovascular accident can include:

- sudden numbness or weakness of the face, arm or leg, especially on one side of the body.
- sudden trouble walking, dizziness, loss of balance or coordination.
- sudden confusion, trouble speaking or understanding.
- sudden trouble seeing in one or both eyes.
- sudden, severe or prolonged headache with no known cause.
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack.

Symptoms of myocardial infarction can include:

- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone.
- discomfort radiating to the back, jaw, throat, arm, stomach.
- feeling of being full, having indigestion or choking.
- sweating, nausea, vomiting or dizziness.
- extreme weakness, anxiety, or shortness of breath.
- rapid or irregular heartbeats.

<u>Risk of bone loss</u>

In some women treated with Relugolix Estradiol & Norethisterone, who had normal bone mineral density (BMD) at start of treatment, a bone loss varying from > 3-8% was reported. Therefore, a DXA scan is recommended after the first 52 weeks of treatment to verify that the patient does not have an unwanted degree of BMD loss, that exceeds the benefit of treatment with Relugolix Estradiol & Norethisterone. The benefits and risks of Relugolix Estradiol & Norethisterone in patients with a history of a low trauma fracture or other risk factors for osteoporosis or bone loss, including those taking medications that may affect BMD, should be considered prior to initiating treatment. It is recommended to perform a DXA scan before commencing treatment with Relugolix Estradiol & Norethisterone in these patients. Relugolix Estradiol & Norethisterone should not be initiated if the risk associated with BMD loss exceeds the potential benefit of the treatment.

Liver tumours or liver disease

Relugolix Estradiol & Norethisterone is contraindicated in women with liver tumours, benign or malignant; or liver disease as long as liver function values have not returned to normal. Treatment must be discontinued if jaundice develops. In clinical trials, asymptomatic transient elevations of serum alanine aminotransferase (ALT) at least 3 times the upper limit of the reference range occurred in < 1% of participants treated with Relugolix Estradiol & Norethisterone. Acute liver test abnormalities may necessitate the discontinuation of Relugolix Estradiol & Norethisterone use until the liver tests return to normal.

Renal impairment

The exposure to relugolix is increased in patients with moderate or severe renal impairment, although no dose adjustment is required. The amount of relugolix removed by haemodialysis is unknown.

Change in menstrual bleeding pattern

Patients must be informed that treatment with Relugolix Estradiol & Norethisterone usually leads to a reduction in menstrual blood loss or amenorrhoea within the first 2 months of treatment. Women receiving Relugolix Estradiol & Norethisterone were likely to have amenorrhoea (51.6%) or cyclic bleeding (15.4%), with the rest (31.9%) having an irregular bleeding pattern at the Week 24 assessment. Furthermore, at the Week 52 assessment 70.6% of women receiving Relugolix Estradiol & Norethisterone were likely to have amenorrhoea. In case of persistent excessive bleeding, patients must notify their physician.

Contraceptive properties of Relugolix Estradiol & Norethisterone

Relugolix Estradiol & Norethisterone provides adequate contraception when used for at least 1 month. However, women of childbearing potential must be advised that ovulation will return rapidly after discontinuing treatment. Therefore, alternative contraception needs to be started immediately after discontinuation of treatment.

Reduced ability to recognize pregnancy

Women who take Relugolix Estradiol & Norethisterone commonly experience amenorrhoea or a reduction in the amount, intensity, or duration of menstrual bleeding. This change in menstrual bleeding pattern may reduce the ability to recognise the occurrence of a pregnancy in a timely manner. Perform pregnancy testing if pregnancy is suspected and discontinue treatment, if pregnancy is confirmed.

Uterine fibroid prolapse or expulsion

Submucosal uterine fibroids are common (15% to 20% of women with uterine fibroids) and some may prolapse through the cervix or be expelled, sometimes with transient worsening of uterine bleeding. Women known or suspected to have submucosal uterine fibroids must be advised regarding the possibility of uterine fibroid prolapse or expulsion when treated with Relugolix Estradiol & Norethisterone, and should contact their physician if severe bleeding reoccurs after bleeding symptoms have improved while being treated with Relugolix Estradiol & Norethisterone.

Depression

Carefully observe women with a history of depression and discontinue Relugolix Estradiol & Norethisterone if depression recurs to a serious degree. Data are limited on the association of Relugolix Estradiol & Norethisterone or other products containing estradiol and progestins with onset of depression or exacerbation of existing depression. Women must be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Hypertension

Although small increases in blood pressure have been reported in women taking Relugolix Estradiol & Norethisterone, clinically relevant increases are rare. However, if sustained clinically significant hypertension develops during the use of Relugolix Estradiol & Norethisterone, hypertension should be treated, and the benefit of continued therapy should be assessed. If treatment with Relugolix Estradiol & Norethisterone is discontinued, use may be resumed if normotensive values can be achieved with antihypertensive treatment.

Gallbladder disease

Conditions such as gallbladder disease, cholelithiasis and cholecystitis have been reported to occur or worsen with estrogen and progestogen use, including Relugolix, Estradiol & Norethisterone, but the evidence of an association with Relugolix Estradiol & Norethisterone is inconclusive.

4.5. Drugs interactions

Recommendations regarding interactions with Relugolix, Estradiol & Norethisterone are based on evaluations of interactions for the individual components.

Potential for other medicinal products to affect the components of Relugolix Estradiol & Norethisterone

Relugolix

Oral P-glycoprotein (P-gp) inhibitors:

Concomitant use of Relugolix Estradiol & Norethisterone with oral P-gp inhibitors is not recommended. Relugolix is a substrate of P-gp and in an interaction study with erythromycin, a P-gp and moderate cytochrome P450 (CYP) 3A4 inhibitor, the area under the curve (AUC) and maximum concentration (Cmax) of relugolix were both increased by 6.2-fold. Concomitant use of P-gp inhibitors may increase the exposure of relugolix, including certain anti-infective medicinal products (e.g. erythromycin, clarithromycin, gentamicin, tetracycline), anti-fungal medicinal products (ketoconazole, itraconazole), antihypertensive medicinal products (e.g. carvedilol, verapamil), antiarrhythmic medicinal products (e.g. amiodarone, dronedarone, propafenone, quinidine), antianginal medicinal products (e.g. ranolazine), cyclosporine, human immunodeficiency virus (HIV) or hepatitis C virus (HCV) protease inhibitors (e.g. ritonavir, telaprevir). If concomitant use with once or twice daily oral P-gp inhibitors is unavoidable (e.g. azithromycin), take Relugolix Estradiol & Norethisterone first, and separate dosing with the P-gp inhibitor by at least 6 hours and monitor patients more frequently for adverse reactions.

Strong cytochrome P450 3A4 (CYP3A4) and/or P-gp inducers:

Co-administration of Relugolix Estradiol & Norethisterone with strong CYP3A4 and/or P-gp inducers is not recommended. In a clinical interaction study with rifampicin, a strong CYP3A4 and P-gp inducer, the Cmax and AUC and of relugolix were reduced by 23% and 55%, respectively. Medicinal products that cause strong CYP3A4 and/or P-gp induction, such as anticonvulsants (e.g. carbamazepine, topiramate, phenytoin, phenobarbital, primidone, oxcarbazepine, felbamate), anti-infective medicinal products (e.g. rifampicin, rifabutin, griseofulvin); St. John's wort (Hypericum perforatum); bosentan and HIV or HCV protease inhibitors (e.g. ritonavir, boceprevir, telaprevir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz), may reduce the plasma concentrations of relugolix and may result in a decrease in therapeutic effects.

CYP3A4 inhibitors

Concomitant use of relugolix with strong CYP3A4 inhibitors devoid of P-gp inhibition (voriconazole) did not increase the exposure of relugolix in a clinically meaningful manner. Furthermore, in a clinical interaction study, concomitant administration with atorvastatin, a weak CYP3A4 enzyme inhibitor, did not change the exposure of relugolix in a clinically meaningful manner.

Estradiol and norethisterone acetate

CYP3A4 inhibitors:

Medicinal products that inhibit the activity of hepatic drug-metabolising enzymes, e.g. ketoconazole, may increase circulating concentrations of the estrogen and norethisterone components in Relugolix Estradiol & Norethisterone.

CYP enzyme inducers:

The metabolism of estrogens and progestogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz). Ritonavir, telaprevir and nelfinavir, although known as strong inhibitors, are also inducers and may decrease the exposure of estrogens and progestogens. Herbal preparations containing St John's Wort (Hypericum perforatum) may induce the metabolism of estrogens and progestogens. Clinically, an increase in estrogen metabolism may lead to decreased effectiveness with regard to protection of bone loss. Therefore, long-term concomitant use of liver enzyme inducers with Relugolix Estradiol & Norethisterone is not recommended.

Potential for the components of Relugolix Estradiol & Norethisterone to affect other medicinal products

Relugolix:

Relugolix is a weak inducer of CYP3A4. After co-administration with daily 40 -mg doses of relugolix, the AUC and Cmax of midazolam, a sensitive CYP3A4 substrate, were decreased by 18% and 26%, respectively. However, based on the clinical study with midazolam, clinically meaningful effects of relugolix on other CYP3A4 substrates are not expected.

Relugolix is an inhibitor of breast cancer resistant protein (BCRP) in vitro, therefore, an interaction study was conducted with rosuvastatin, a BCRP and organic anion transporting polypeptide 1B1 (OATP1B1) substrate. After co-administration with daily 40-mg doses of relugolix, the AUC and Cmax of rosuvastatin were decreased by 13% and 23%, respectively. The effects are not considered clinically meaningful and therefore no dose-adjustments of rosuvastatin upon concomitant use are recommended. Clinical effects of Relugolix Estradiol & Norethisterone on other BCRP substrates have not been evaluated and the relevance for other BCRP substrates is unknown.

Relugolix may cause saturation of intestinal P-gp at the 40 mg dose, as relugolix exhibits more than dose proportional pharmacokinetics over the dose range of 10-120 mg, which could result in increased absorption of co-administered medicines that are sensitive substrates of P-gp. No clinical interaction studies have been conducted with P-gp substrates such as dabigatran etexilate or fexofenadine. Therefore, co-administration with sensitive P-gp substrates is not recommended.

Estradiol and norethisterone acetate:

Estrogen and progestogen medicinal products may affect the metabolism of certain other active substances. Accordingly, plasma concentrations may either increase (e.g. cyclosporin) or

decrease (e.g. lamotrigine) with use of Relugolix Estradiol & Norethisterone. Dose adjustment of these medicinal products may be necessary.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Women of childbearing potential

Relugolix Estradiol & Norethisterone inhibits ovulation in women taking the recommended dose and provides adequate contraception. A nonhormonal contraceptive method is recommended for use for 1 month after initiation of treatment and for 7 days following 2 or more missed consecutive doses. Concomitant use of hormonal contraceptives is contraindicated. Women of childbearing potential must be advised that ovulation will return rapidly after discontinuing Relugolix Estradiol & Norethisterone. A discussion with the patient, regarding appropriate contraceptive methods, must therefore take place prior to discontinuing treatment and alternative contraception needs to be started immediately after discontinuation of treatment.

Pregnancy

There is a limited amount of data from the use of relugolix in pregnant women. Studies in animals have shown that exposure to relugolix early in pregnancy may increase the risk of early pregnancy loss Based on the pharmacological effects, an adverse effect on pregnancy cannot be excluded. Relugolix Estradiol & Norethisterone is contraindicated during pregnancy. Discontinue use of treatment if pregnancy occurs. There appears to be little or no increased risk of harmful effects in children born to women who have used estrogens and progestogens as an oral contraceptive inadvertently during early pregnancy. The increased risk of VTE during the postpartum period must be considered when re-starting Relugolix Estradiol & Norethisterone.

Breast-feeding

Results from nonclinical studies indicate that relugolix is excreted into the milk of lactating rats.

No data are available regarding the presence of relugolix or its metabolites in human milk or its effect on the breastfed infant. Detectable amounts of estrogen and progestogens have been identified in the breast milk of women receiving estrogen plus progestogen therapy. An effect on breastfeeding newborns/infants cannot be excluded. Breastfeeding is contraindicated during the use of Relugolix Estradiol & Norethisterone and for 2 weeks following discontinuation of Relugolix Estradiol & Norethisterone.

Fertility

Relugolix Estradiol & Norethisterone inhibits ovulation and often causes amenorrhoea. Ovulation and menstrual bleeding will return rapidly after discontinuing treatment.

4.7. Effects on ability to drive and use machines

Relugolix Estradiol & Norethisterone has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Summary of the safety profile

The most frequent adverse drug reactions were hot flush (8.3%) and uterine bleeding (4.7%).

Tabulated list of adverse drug reactions

Adverse drug reactions listed in Table 3 are classified according to frequency and system organ class. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), and not known (cannot be estimated from available data).

Table. Adverse drug reactions

Psychiatric disorders	
Common	Irritability
Vascular disorders	
Common	Hot flush
Gastrointestinal disorders	
Common	Dyspepsia
Skin and subcutaneous tissue disorders	
Common	Alopecia HyperhidrosisNight sweats
Uncommon	Angioedema Urticaria
Reproductive system and breast disorders	
Common	Uterine bleeding* Breast cyst Libido decreased
Uncommon	Uterine myoma expulsion

* includes menorrhagia and metrorrhagia

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

Single doses of relugolix up to 360 mg (9 times the recommended clinical dose of 40 mg) have been administered to healthy men and women and were generally well tolerated. 11 Overdoses up to 2 times the recommended dose have been reported during the clinical development of relugolix in combination with estradiol and norethisterone acetate without reports of adverse events. Supportive care is recommended if an overdose occurs. The amount of relugolix, estradiol or norethisterone removed by haemodialysis is unknown. Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdose of estradiol and norethisterone acetate may cause nausea and vomiting, and withdrawal bleeding may occur in women.

5. Pharmacological properties

5.1. Mechanism of Action

Relugolix is a non-peptide GnRH receptor antagonist that binds to and inhibits GnRH receptors in the anterior pituitary gland. In humans, inhibition of GnRH receptor results in a dose dependent decrease in the release of luteinizing hormone (LH) and follicle-stimulating

hormone (FSH) from the anterior pituitary gland. As a result, circulating concentrations of LH and FSH are reduced. The reduction in FSH concentrations prevents follicular growth and development, thereby reducing the production of estrogen. Prevention of an LH surge inhibits ovulation and development of the corpus luteum, which precludes the production of progesterone. Therefore, Relugolix Estradiol & Norethisterone provides adequate contraception when taken for at least 1 month.

Estradiol is the same as the endogenously produced hormone and is a potent agonist of the nuclear estrogen receptor (ER) subtypes. Exogenously administered estradiol alleviates symptoms associated with a hypoestrogenic state, such as vasomotor symptoms and bone mineral density loss.

Norethisterone acetate is a synthetic progestogen. As estrogens promote the growth of the endometrium, unopposed estrogens increase the risk of endometrial hyperplasia and cancer. The addition of a progestogen reduces the estrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

5.2. Pharmacodynamic properties

Effects on pituitary and ovarian hormones After administration of relugolix, rapid, dose-dependent decreases in circulating concentrations of LH, FSH, and estradiol are observed. Near maximum decreases in estradiol concentrations is noted with a 40-mg dose to within the postmenopausal range. Across clinical studies, average estradiol concentrations were consistently maintained at least 10 pg/mL higher with Relugolix Estradiol & Norethisterone compared with relugolix alone. In the phase 3 clinical studies with Relugolix Estradiol & Norethisterone, median estradiol predose concentrations after 24 weeks were approximately 33 pg/mL, corresponding with estradiol concentrations associated with the early follicular phase of the menstrual cycle. Progesterone levels were maintained at < 3.0 ng/mL with Relugolix Estradiol & Norethisterone.

Effects on ovulatory function

In a single cohort study in healthy premenopausal women, administration of Relugolix Estradiol & Norethisterone once daily for 84 days substantially suppressed follicular growth throughout the 84-day treatment period (mean dominant follicle size of approximately 6 mm) and ovulation was inhibited in 100% of women as assessed by the Hoogland-Skouby score. After discontinuation of treatment, all women assessed (66 of 67) returned to ovulation within 43 days (mean 23.5 days).

Efficacy and safety over 24 weeks

The efficacy and safety of Relugolix Estradiol & Norethisterone once daily was assessed in two replicate, 24-week, multinational, randomised, double-blind, placebo-controlled studies in patients aged 18 – 50 with heavy menstrual bleeding associated with uterine fibroids. Patients were required to have uterine fibroids confirmed by ultrasound and menstrual blood loss (MBL) volume of ≥ 80 mL, as assessed by the alkaline hematin method.

5.3. Pharmacokinetic properties

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1), and norethisterone (NET) following oral administration of a single Relugolix Estradiol & Norethisterone tablet to healthy postmenopausal women under fasted conditions are summarized in Table.

Table. Single dose pharmacokinetic parameters of relugolix, estradiol, total estrone, and norethisterone in post-menopausal women

	Relugolix	Estradiol (E2)	Unconjugated Estrone (E1)	Norethisterone (NET)
AUC0-∞ (ng*hr/mL or pg*hr/mL)	198.1 (111.6)	818.7 (334.4)	4126 (1650)	17.5 (8.46)
Cmax (ng/mL or pg/mL)	25.99 (18.21)	27.95 (19.15)	188.4 (59.09)	3.57 (1.43)
Tmax (hr)	2.00 (0.25, 5.00)	7.00 (0.25, 24.00)	6.00 (2.00, 12.00)	1.01 (0.50, 4.00)
Terminal t1/2 (hr)	61.5 (13.2)	16.6 (7.67)	15.9 (6.52)	10.9 (3.05)

Abbreviations: AUC0-∞ = area under the concentration-time curve from time 0 extrapolated to infinity;

Cmax = maximum observed concentration; E1 = estrone; E2 =estradiol; NET = norethisterone; Tmax = time to the maximum observed concentration; t1/2 = half-life

Note: Baseline-adjusted pharmacokinetic parameters for estradiol and unconjugated E1 are presented in this table. Arithmetic means and standard deviations are shown except for tmax, where median and range (minimum, maximum) are shown. AUC0-∞ is presented in ng*hr/mL for relugolix and NET and in pg*hr/mL for unconjugated E2 and unconjugated E1. Cmax is presented in ng/mL for relugolix and NET and in pg/mL for unconjugated E2 and unconjugated E1.

The pharmacokinetic parameters of relugolix, estradiol (E2), total estrone (E1), and norethisterone (NET) at steady state after once daily administration of Relugolix Estradiol & Norethisterone for 6 weeks to healthy premenopausal women are summarized in Table.

Table. Multi-dose pharmacokinetic parameters of relugolix, estradiol, total estrone, and norethisterone in pre-menopausal women

	Relugolix	Estradiol (E2)	Unconjugated Estrone (E1)	Norethisterone (NET)
AUC0-24 (ng*hr/mL or pg*hr/mL)	157 (94.7)	784 (262)	4450 (1980)	25.5 (11.4)
Cmax (ng/mL or pg/mL)	26 (21.4)	46.8 (17.3)	303 (137)	5.21 (1.53)
Tmax (hr)	3 (0.5, 6)	3 (0.50, 12.00)	4 (1, 8.08)	1 (1, 2)
Effective t1/2 (hr)	~25	17.1 (4.03)	13.9 (4.14)	8.28 (1.87)

Abbreviations: AUC0-24 = area under the concentration-time curve during a dosing interval (24); Cmax = maximum observed concentration; E1 = estrone; E2 =estradiol; NET = norethisterone; tmax = time to the maximum observed concentration. Note: arithmetic means and standard deviations are shown except for tmax, where median and range (minimum, maximum) are shown. AUC0-24 is presented in ng*hr/mL for relugolix and NET and in pg*hr/mL for unconjugated E2 and unconjugated E1. Cmax is presented in ng/mL for relugolix and NET and in pg/mL for unconjugated E2 and unconjugated E1. Effective half-life for relugolix is estimated from accumulation ratios based on AUC values after multiple-dose administration of relugolix at 40 mg.

Absorption

The absorption of relugolix after oral administration is primarily mediated by the P-gp efflux transporter, for which relugolix is a substrate. After oral administration, relugolix is rapidly absorbed, reaching an initial peak by 0.25 hours postdose followed by one or more subsequent absorption peaks through up to 12 hours postdose. The absolute bioavailability of relugolix is 11.6%. After administration of Relugolix Estradiol & Norethisterone with a high-fat, high-calorie meal, the AUC0-∞ and Cmax of relugolix were decreased by 38% and 55%, respectively, compared with the fasted state. After oral administration of a single dose of Relugolix Estradiol & Norethisterone in the fasted state, unconjugated estradiol concentrations increased slowly with mean concentrations reaching peak concentrations at 8 hours postdose. After administration of Relugolix Estradiol & Norethisterone following consumption of a high-fat, high-calorie meal, no clinically meaningful effects of food on the exposure to estradiol or estrogenic metabolites were observed. After oral administration, norethisterone acetate undergoes rapid biotransformation in the intestine and liver to norethisterone (NET). After oral administration of a single dose of Relugolix Estradiol & Norethisterone in the fasted state, NET concentrations were initially quantifiable at 0.5 hours postdose, increasing rapidly thereafter with mean concentrations reaching peak concentrations within 1 hour. Food effects Administration with food reduced the AUC and Cmax of relugolix by 38% and 55%, respectively, relative to fasted conditions; however, the decrease in exposure to relugolix is considered not to be clinically meaningful. No clinically meaningful effects of food on the exposure to estradiol, estrogenic metabolites, or norethisterone were observed.

Distribution

Relugolix is 68% to 71% bound to human plasma proteins with a mean whole blood-to-plasma ratio of 0.78. Estradiol and norethisterone circulating in the blood bind to a similar extent to sex hormone- 16 binding globulin (SHBG; 36% to 37%) and to albumin (61%), while only approximately 1-2% are unbound. The value for apparent volume of distribution (Vz) of 19 x 103 L derived from the absolute bioavailability study after intravenous administration indicates that relugolix distributes widely into tissues. The distribution of exogenous and endogenous estradiol is similar. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex hormone target organs.

Biotransformation

In vitro studies indicate that the primary CYP enzymes contributing to the overall hepatic oxidative metabolism of relugolix were CYP3A4/5 (45%) > CYP2C8 (37%) > CYP2C19 (< 1%) with the oxidative metabolites, metabolite-A and metabolite-B, formed by CYP3A4/5 and CYP2C8, respectively. The metabolism of exogenous and endogenous estradiol is similar. Metabolism of estradiol occurs mainly in the liver and the gut but also in target organs and involves the formation of less active or inactive metabolites, including estrone, catecholestrogens and several estrogen sulphates and glucuronides. Estrogens are excreted with the bile, hydrolysed and reabsorbed (enterohepatic circulation), and mainly eliminated in urine in biologically inactive form. Oxidation of estrone and estradiol involves cytochrome P450 enzymes, mainly CYP1A2, CYP1A2 (extra hepatic), CYP3A4, CYP3A5, and CYP1B1 and CYP2C9.

Elimination

Once absorbed, approximately 20% of relugolix is eliminated as unchanged active substance in the urine and 80% is eliminated through metabolism by multiple minor metabolic pathways and/or biliary secretion of unchanged active substance. Approximately 38% of the administered dose is excreted as metabolites (other than Metabolite-C) in the faeces and urine. Metabolite-C, which is formed by intestinal microflora, is the primary metabolite in faeces

(51%) and further reflects non-absorbed active substance. The mean terminal phase elimination half-life (t1/2) of relugolix, estradiol, and norethisterone following single-dose administration of the Relugolix Estradiol & Norethisterone tablet are 61.5 hours, 16.6 hours, and 10.9 hours, respectively. Steady state of relugolix is reached after 12 to 13 days of once daily administration. The degree of accumulation of relugolix upon once daily administration is approximately 2-fold, reflecting an effective half-life of approximately 25 hours and supporting once daily administration of relugolix. The accumulation for E2 and NET upon once daily administration are reported to be 33% to 47%, although when co-administered with relugolix, a weak inducer of intestinal (pre-systemic) CYP3A-mediated metabolism, the accumulation for E2 is expected to be similar or slightly lower.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Non-clinical studies have not been conducted with relugolix in combination with estradiol and norethisterone acetate. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.

Reproductive toxicity and development

In pregnant rabbits orally dosed with relugolix during the period of organogenesis, spontaneous abortion and total litter loss were observed at exposure levels (AUC) comparable to that achieved at the recommended human dose of 40 mg/day. No effects on embryofoetal development were observed in rats; however, relugolix does not interact significantly with GnRH receptors in that species. In experimental animals, estradiol or estradiol valerate displayed an embryo lethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male foetuses were observed. Norethisterone, like other progestogens, caused virilisation of female foetuses in rats and monkeys. After high doses of norethisterone, embryo lethal effects were observed.

Lactation

In lactating rats administered a single oral dose of 30 mg/kg radiolabelled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose decreasing to low levels by 48 hours post-dose. The majority of relugolix-derived radioactivity in milk consisted of unchanged relugolix

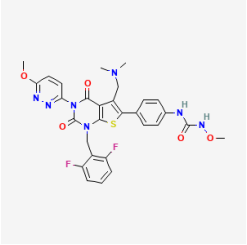
Environmental risk assessment (ERA)

Environmental risk assessment studies have shown that relugolix may pose a risk for the aquatic compartment

7. Description

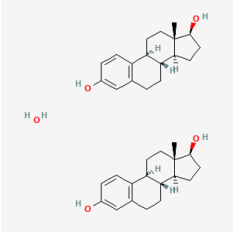
Relugolix:

Relugolix is 1-[4-[1-[(2,6-difluorophenyl)methyl]-5-[(dimethylamino)methyl]-3-(6-methoxypyridazin-3-yl)-2,4-dioxothieno[2,3-d]pyrimidin-6-yl]phenyl]-3-methoxyurea. The empirical formula is $C_{29}H_{27}F_2N_7O_5S$ and it has a molecular weight of 623.6 g/mol. The chemical structure of Relugolix is:



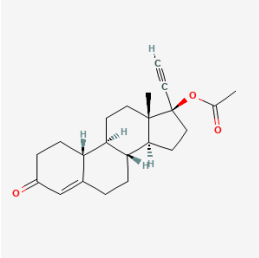
Estradiol Hemihydrate:

Estradiol Hemihydrate is bis((8R,9S,13S,14S,17S)-13-methyl-6,7,8,9,11,12,14,15,16,17-decahydrocyclopenta[a]phenanthrene-3,17-diol);hydrate. The empirical formula is $C_{36}H_{50}O_5$ and it has a molecular weight of562.8 g/mol. The chemical structure of Estradiol Hemihydrate:



Norethindrone Acetate:

Norethindrone Acetate is [(8R,9S,10R,13S,14S,17R)-17-ethynyl-13-methyl-3-oxo-1,2,6,7,8,9,10,11,12,14,15,16-dodecahydrocyclopenta[a]phenanthren-17-yl] acetate. The empirical formula is $C_{22}H_{28}O_3$ and it has a molecular weight of 340.5 g/mol. The chemical structure of Norethindrone Acetate is:



Regestrone LX

Relugolix, Estradiol and Norethindrone Acetate Tablets are yellow color rounds, biconvex, both side plain, film coated tablets. Packed in PVC and Plain aluminium foil. The list of excipients used are Lactose, Starch, Crospovidone, Sodium Lauryl sulphate, Sodium Starch Glycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Hydroxypropyl Methylcellulose, Polyethylene Glycol, Titanium Dioxide, Talcum powder and Ferric oxide Yellow.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than Date of Expiry.

8.3. Packaging information

Regesterone LX is packed in blister strips of 28 tablets.

8.4. Storage and handing instructions

Store in a cool and dry Place at temperature 15-30^{o} C

Dosage: As directed by the Physician.

Keep all medicines out of reach of children.

The drug should be sold by retail under prescription of Gynecologist only.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Akums Drugs & Pharmaceuticals Ltd.
Plot No. 47 & 48, Sector-6a, I.I.E.,
Sidcul, Ranipur, Haridwar-249 403,
Uttarakhand, India.

11. Details of permission or licence number with date

Mfg. Lic. No. 97/UA/SC/P-2009 Issued on 11.12.2025.

12. Date of revision

NA

MARKETED BY

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