ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions

1. NAME OF THE MEDICINAL PRODUCT

Orgovyx 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 120 mg of relugolix.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Light red, almond-shaped, film-coated tablet (11 mm [length] × 8 mm [width]) with "R" on one side and "120" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Orgovyx is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer.

4.2 Posology and method of administration

Treatment with Orgovyx should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.

Posology

Treatment with Orgovyx should be initiated with a loading dose of 360 mg (three tablets) on the first day, followed by a 120 mg (one tablet) dose taken once daily at approximately the same time each day.

Because relugolix does not induce an increase in testosterone concentrations, it is not necessary to add an anti-androgen as surge protection at initiation of therapy.

Dose modification for use with P-gp inhibitors
Co-administration of Orgovyx with oral P-glycoprotein (P-gp) inhibitors must be avoided. If co-administration is unavoidable, Orgovyx should be taken first and dosing should be separated by at least 6 hours (see section 4.5). Treatment with Orgovyx may be interrupted for up to 2 weeks if a short course of treatment with a P-gp inhibitor is required.

Dose modification for use with combined P-gp and strong CYP3A inducers
Co-administration of Orgovyx with combined P-gp and strong cytochrome P450 (CYP) 3A inducers must be avoided. If co-administration is unavoidable, the dose of Orgovyx must be increased to 240 mg once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, the recommended 120 mg dose of Orgovyx once daily must be resumed (see section 4.5).

Missed doses

If a dose is missed, Orgovyx must be taken as soon as the patient remembers. If the dose was missed by more than 12 hours, the missed dose must not be taken and regular dosing schedule should be resumed the following day.

If treatment with Orgovyx is interrupted for greater than 7 days, Orgovyx must be restarted with a loading dose of 360 mg on the first day, followed with a dose of 120 mg once daily.

Special populations

Elderly
No dose adjustment in elderly patients is required (see section 5.2).

Renal impairment
No dose adjustment in patients with mild, or moderate renal impairment is required. Caution is warranted in patients with severe renal impairment (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment in patients with mild or moderate hepatic impairment is required (see sections 4.4 and 5.2).

Paediatric population
There is no relevant use of Orgovyx in children and adolescents under 18 years of age for the indication of treatment of advanced hormone-sensitive prostate cancer.

Method of administration

Oral use.

Orgovyx can be taken with or without food (see section 5.2). Tablets should be taken with some liquid as needed and should be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect on QT/QTc interval prolongation

Androgen deprivation therapy may prolong the QT interval.
In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval (see section 4.5), physicians should assess the benefit-risk ratio including the potential for Torsade de pointes prior to initiating Orgovyx.

A thorough QT/QTc study showed that there was no intrinsic effect of relugolix on prolongation of the QTc interval (see section 4.8).

Cardiovascular disease

Cardiovascular disease such as myocardial infarction and stroke has been reported in the medical literature in patients with androgen deprivation therapy. Therefore, all cardiovascular risk factors should be taken into account.

Changes in bone density

Long-term suppression of testosterone in men who have had orchiectomy or who have been treated with a GnRH receptor agonist or GnRH antagonist is associated with decreased bone density. Decreased bone density, in patients with additional risk factors, may lead to osteoporosis and increased risk of bone fracture.

Hepatic impairment

Patients with known or suspected hepatic disorder have not been included in long-term clinical trials with relugolix. Mild, transient increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been observed but were not accompanied by an increase in bilirubin or associated with clinical symptoms (see section 4.8). Monitoring of liver function in patients with known or suspected hepatic disorder is advised during treatment. The pharmacokinetics of relugolix in patients with severe hepatic impairment has not been evaluated (see section 5.2).

Severe renal impairment

The exposure to relugolix in patients with severe renal impairment may be increased by up to 2-fold (see section 5.2). Because a lower dose of relugolix is not available, caution in patients with severe renal impairment is warranted upon administration of a 120-mg dose of relugolix once daily. The amount of relugolix removed by haemodialysis is unknown.

Prostate-specific antigen (PSA) monitoring

The effect of Orgovyx should be monitored by clinical parameters and prostate-specific antigen (PSA) serum levels.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect the exposure to relugolix

P-gp inhibitors

Co-administration of Orgovyx and oral P-gp inhibitors should be avoided. Relugolix is a P-gp substrate (see section 5.2). Upon co-administration of a 120-mg dose of relugolix following administration of 500-mg doses of erythromycin four times daily for 8 days, a moderate P-gp and moderate CYP3A inhibitor, the area under the plasma concentration-time curve (AUC) and maximum plasma concentration (C_{max}) of relugolix was increased by 3.5- and 2.9-fold, respectively, due to inhibition of intestinal P-gp by erythromycin, which resulted in an increase in the oral bioavailability of relugolix.

Upon co-administration of a 120 mg dose of relugolix and a single 500 mg dose of azithromycin, a weak P-gp inhibitor, the AUC and C_{max} of relugolix were increased by 1.5- and 1.6-fold, respectively, although in the median concentration-time curves increases in relugolix exposure up to 5-fold were observed 1-3 hours after dosing. When the single dose of azithromycin was administered 6 hours after the 120 mg relugolix dose, the AUC and Cmax of relugolix were increased by 1.4- and 1.3-fold, respectively (see Table 1); the increase in relugolix exposure in the median concentration-time curves was maximally 1.6-fold in the window 1-3 hours after dosing. Due to limited number of subjects (n=18) and high PK variability, confidence intervals around these increases were wide (for AUC from 1.0- to 2.1-fold).

Co-administration of Orgovyx with other oral P-gp inhibitors also may increase the AUC and C_{max} of relugolix and may therefore increase the risk of adverse reactions associated with Orgovyx. Medicinal products that are oral P-gp inhibitors include certain anti-infectives (e.g. azithromycin, erythromycin, clarithromycin, gentamicin, tetracycline), antifungal agents (ketoconazole, itraconazole), antihypertensives (e.g. carvedilol, verapamil), antiarrhythmics (e.g. amiodarone, dronedarone, propafenone, quinidine), antianginal agents (e.g. ranolazine), cyclosporine, human immunodeficiency virus (HIV) or hepatitis C virus (HCV) protease inhibitors (e.g. ritonavir, telaprevir).

If co-administration with once or twice daily oral P-gp inhibitors cannot be avoided, Orgovyx should be taken first, with the oral P-gp inhibitor taken 6 hours thereafter, and patients should be monitored more frequently for adverse reactions. Alternatively, treatment with Orgovyx may be interrupted for up to 2 weeks for a short course of treatment with a P-gp inhibitor (e.g. for certain macrolide antibiotics). If treatment with Orgovyx is interrupted for more than 7 days, resume administration of Orgovyx with a 360 mg loading dose on the first day followed by 120 mg once daily (see section 4.2).

Combined P-gp and strong CYP3A inducers

Co-administration of Orgovyx with combined P-gp and strong CYP3A inducers should be avoided. Upon co-administration of a 40-mg dose of relugolix following administration of 600-mg doses of rifampicin once daily for 13 days, a P-gp and strong CYP3A inducer, the AUC and C_{max} of relugolix were decreased by 55% and 23%, respectively, due to induction of intestinal P-gp (and CYP3A) by rifampicin, which resulted in a decrease in the oral bioavailability of relugolix. Co-administration of Orgovyx with other combined P-gp and strong CYP3A inducers also may decrease the AUC and C_{max} of relugolix and may therefore reduce the therapeutic effects of Orgovyx. Medicinal products that are combined P-gp and strong CYP3A4 inducers include the androgen receptor inhibitor apalutamide, certain anticonvulsants (e.g. carbamazepine, phenytoin, phenobarbital), anti-infectives (e.g. rifampicin, rifabutin), St. John's Wort (*Hypericum perforatum*), HIV or HCV protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz).

If co-administration cannot be avoided, the Orgovyx dose should be increased (see section 4.2). After discontinuation of the combined P-gp and strong CYP3A inducer, the recommended dose of Orgovyx should be resumed once daily.

Other medicinal products

No clinically significant differences in the pharmacokinetics of relugolix were observed upon co-administration of relugolix with voriconazole (strong CYP3A inhibitor; 400-mg doses twice daily on the first day followed by 200-mg doses twice daily for 8 days), atorvastatin (80-mg doses once daily for 10 days), or acid-reducing agents. No clinically significant differences in the pharmacokinetics of a single 5-mg dose of midazolam (sensitive CYP3A substrate) or a single dose of 10-mg of rosuvastatin (breast cancer resistance protein [BCRP] substrate) were observed upon co-administration with relugolix. Based on limited data (n=20) in men who received a 120-mg dose of relugolix and 80- to 160-mg doses of enzalutamide (an androgen receptor signalling inhibitor that is a strong CYP3A inducer and P-gp inhibitor) concomitantly for up to 266 days in the phase 3 study, plasma relugolix trough and serum testosterone concentrations did not change to a clinically significant extent upon adding enzalutamide to the relugolix monotherapy. Therefore, the same dose of relugolix may be maintained during combination treatment.

Since androgen deprivation treatment may prolong the QT interval, the concomitant use of Orgovyx with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

Effect of co-administered medicinal products on the exposure to relugolix from clinical trials and associated dosing recommendations are summarised in Table 1.

Table 1. Effect of co-administered medicinal products on relugolix exposure (C_{max}, $AUC_{0\text{-}inf}$) from clinical trials and recommendations

Interacting drug dose regimen	Relugolix dose regimen	Change in relugolix $AUC_{0\text{-}inf}$	Change in relugolix C_{max}	Recommendation
erythromycin 500 mg QID, multiple doses	120 mg single dose	3.5 -fold ↑	2.9 -fold ↑	Concomitant use of Orgovyx with erythromycin and other oral P-gp inhibitors is not recommended If concomitant use with once or twice daily oral P-gp inhibitors is unavoidable (e.g. azithromycin), take Orgovyx first, and separate dosing with the P-gp inhibitor by at least 6 hours and monitor patients more frequently for adverse reactions.
azithromycin 500 mg single dose	120 mg single dose	1.5 -fold ↑	1.6 -fold ↑	If concomitant use with once or twice daily oral P-gp inhibitors is unavoidable (e.g. azithromycin), take Orgovyx first, and separate dosing with the P-gp inhibitor by at least 6 hours and monitor patients more frequently for adverse reactions.
azithromycin 500 mg single dose 6 hours after administration of relugolix		1.4 -fold ↑	1.3 -fold ↑	
voriconazole 200 mg BID, multiple doses	120 mg single dose	12% ↑	18% ↓	No dose modifications recommended for co-administration of relugolix and CYP3A4 inhibitors devoid of P-gp inhibition
fluconazole 200 mg QD, multiple doses	40 mg single dose	19%↑	44% ↑	
atorvastatin 80 mg QD, multiple doses	40 mg single dose	5%↓	22%↓	
rifampicin 600 mg QD, multiple doses	40 mg single dose	55%↓	23%↓	Co-administration of Orgovyx with rifampicin and other strong CYP3A4 and/or P-gp inducers is not recommended

Potential for relugolix to affect the exposure to other medicinal products

Relugolix is a weak inducer of CYP3A-mediated metabolism. Upon co-administration of a single 5-mg dose of midazolam, a sensitive CYP3A substrate, following once daily administration of 120-mg doses of Orgovyx to steady state, the $AUC_{0\text{-}inf}$ and C_{max} of midazolam was decreased by 22% and 14%, respectively, which is not considered to be clinically meaningful. Clinically meaningful effects on other CYP3A4 substrates are not expected; however, if a decrease in the therapeutic effects occur, medicinal products (e.g. statins) may be titrated to achieve desired therapeutic effects.

Relugolix is an inhibitor of BCRP *in vitro*. Upon co-administration of a single 10-mg dose of rosuvastatin, a BCRP and OATP1B1 substrate, following once daily administration of 120-mg doses of relugolix to steady state, the $AUC_{0\text{-}inf}$ and C_{max} of rosuvastatin were decreased by 27% and 34%, respectively. The decrease in exposure to rosuvastatin is not considered clinically meaningful; however, rosuvastatin may be titrated to achieve desired therapeutic effects. The effect of relugolix on other BCRP substrates has not been evaluated and the relevance for other BCRP substrates is unknown.

Relugolix is an inhibitor of P-gp *in vitro*. However, upon co-administration of a single 150 mg dose of dabigatran etexilate, a P-gp substrate, with a single 120 mg dose of relugolix, the $AUC_{0\text{-}inf}$ and C_{max} of total dabigatran was increased by 17% and 18%, respectively, which is not considered to be clinically meaningful. Therefore, clinically meaningful effects of a 120 mg dose relugolix on other P-gp substrates are not expected.

Considering that the 360 mg loading dose of relugolix has not been tested, dose separation of the loading dose of relugolix from administration of other P-gp substrates is advised.

In vitro studies
Cytochrome P450 (CYP) enzymes: Relugolix is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 nor an inducer of CYP1A2 or CYP2B6 at clinically relevant plasma concentrations.

Transporter systems: Relugolix is not an inhibitor of OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT2, MATE1, MATE2-K, or BSEP at clinically relevant plasma concentrations.

4.6 Fertility, pregnancy and lactation

This medicinal product is not indicated in women of childbearing potential. It is not to be used in women who are, or may be, pregnant or breast-feeding (see section 4.1).

Contraception

It is not known whether relugolix or its metabolites are present in semen. Based on findings in animals and mechanism of action, if a patient engages in sexual intercourse with a woman of childbearing potential, effective contraception during treatment and for 2 weeks after the last dose of Orgovyx must be used.

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 in early pregnancy may increase the risk of early pregnancy loss (see section 5.3). Based on the pharmacological effects, an adverse effect on pregnancy cannot be excluded.

Breast-feeding

Results from nonclinical studies indicate that relugolix is excreted into the milk of lactating rats (see section 5.3). No data are available regarding the presence of relugolix or its metabolites in human milk or its effect on the breast-fed infant. An effect on breast-feeding newborns/infants cannot be excluded.

Fertility

Based on findings in animals and mechanism of action, Orgovyx may impair fertility in males of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

Orgovyx has no or negligible influence on the ability to drive and use machines. Fatigue and dizziness are very common (fatigue) and common (dizziness) adverse reactions that may influence the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly observed adverse reactions during relugolix therapy are physiological effects of testosterone suppression, including hot flushes (54%), musculoskeletal pain (30%), and fatigue (26%). Other very common adverse reactions include diarrhoea and constipation (12% each).

Tabulated list of adverse reactions

Adverse reactions listed in Table 2 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). Within each frequency group, adverse reactions are presented in order of decreasing seriousness.

Table 2. Adverse reactions reported in the HERO study

Blood and lymphatic system disorders	
Common	Anaemia
Endocrine disorders	
Common	Gynaecomastia
Psychiatric disorders	
Common	Insomnia
	Depression
Nervous system disorders	
Common	Dizziness
	Headache
Cardiac disorders	
Rare	Myocardial infarction
Unknown	QT prolonged (see sections 4.4 and 4.5)
Vascular disorders	
Very common	Hot flush
Common	Hypertension
Gastrointestinal disorders	
Very common	Diarrhoea[a]
	Constipation
Common	Nausea
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
	Rash
Uncommon	Urticaria
	Angioedema
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain[b]
Uncommon	Osteoporosis/osteopenia
Reproductive and breast disorders	
Common	Libido decreased
General disorder and administration site conditions	

Very common	Fatigue[c]
Investigations	
Common	Weight increased
	Glucose increased[d]
	Triglyceride increased[d]
	Blood cholesterol increased[e]
Uncommon	Aspartate aminotransferase increased
	Alanine aminotransferase increased[d]

[a] Includes diarrhoea and colitis
[b] Includes arthralgia, back pain, pain in extremity, musculoskeletal pain, myalgia, bone pain, neck pain, arthritis, musculoskeletal stiffness, non-cardiac chest pain, spinal pain, and musculoskeletal discomfort
[c] Includes fatigue and asthenia
[d] Grade 3/4 increases identified through clinical laboratory test monitoring (see below)
[e] There were no reported cholesterol increases > grade 2

Description of selected adverse reactions

Changes in laboratory parameters
Changes in laboratory values observed during up to 1 year of treatment in the phase 3 study (N = 622) were in the same range for Orgovyx and a GnRH agonist (leuprorelin) used as active comparator. ALT and/or AST concentrations > 3x upper limit of normal (ULN) were reported for 1.4% of patients with normal values prior to treatment, following treatment with Orgovyx. An increase to grade 3/4 ALT was observed in 0.3% of patients and to grade 3/4 AST in 0% of patients treated with Orgovyx, respectively. No events were associated with increased bilirubin.

Haemoglobin concentration decreased by 10 g/L during up to 1 year of treatment. Marked decrease in haemoglobin (≤ 105 g/L) was observed in 4.8% following treatment with Orgovyx, with decreases to grade 3/4 in 0.5%. Glucose increased to grade 3/4 in 2.9% and triglycerides increased to grade 3/4 in 2.0% of patients observed.

Reporting of suspected 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no known specific antidote for overdose with Orgovyx. In the event of an overdose, Orgovyx should be stopped and general supportive measures should be undertaken until any clinical toxicity has diminished or resolved, taking into consideration the half-life of 61.5 hours. Adverse reactions in the event of an overdose have not yet been observed; it is expected that such reactions would resemble the adverse reactions listed in section 4.8. It is not known if relugolix is removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, other hormone antagonists and related agents, ATC code: L02BX04

Mechanism of action

Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to GnRH receptors in the anterior pituitary gland preventing native GnRH from binding and signalling the secretion of

luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Consequently, the production of testosterone from the testes is reduced. In humans, FSH and LH concentrations rapidly decline upon initiating treatment with Orgovyx and testosterone concentrations are suppressed to below physiologic concentrations. Treatment is not associated with the initial increases in FSH and LH concentrations and subsequently testosterone ("potential symptomatic flare") observed upon initiation of treatment with a GnRH analogue. Following discontinuation of treatment, pituitary and gonadal hormone concentrations return to physiologic concentrations.

Clinical efficacy and safety

The safety and efficacy of Orgovyx was evaluated in HERO, a randomised, open-label study in adult men with androgen-sensitive advanced prostate cancer requiring at least 1 year of androgen deprivation therapy and who were not candidates for surgical or radiation therapy with curative intent. Eligible patients had either evidence of biochemical (PSA) or clinical relapse following local primary intervention with curative intent and were not candidates for salvage surgery, had newly diagnosed androgen-sensitive metastatic disease, or had advanced localized disease unlikely to be cured by primary intervention with either surgery or radiation. Eligible patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients with disease progression during the treatment period were encouraged to remain on study and, if indicated, may have received radiotherapy as prescribed by the investigator. If PSA levels rose, patients were allowed to receive enzalutamide after the confirmation of PSA progression or docetaxel during the study.

The primary efficacy outcome measure was medical castration rate defined as achieving and maintaining serum testosterone suppression to castrate levels (< 50 ng/dL) by day 29 through 48 weeks of treatment, plus non-inferiority of relugolix compared to leuprorelin was assessed (see Table 3). Other key secondary endpoints included castration rates on day 4 and 15, castration rates with testosterone < 20 ng/dL at day 15, and PSA response rate at day 15 (see Table 4).

A total of 934 patients were randomised to receive Orgovyx or leuprorelin in a 2:1 ratio for 48 weeks:

a) Orgovyx at a loading dose of 360 mg on the first day followed by daily doses of 120 mg orally.
b) Leuprorelin 22.5 mg injection (or 11.25 mg in Japan, Taiwan, and China) subcutaneously every 3 months. Leuprorelin acetate 11.25 mg every 3 months is a dosage regimen that is not recommended for this indication in the European Union.

The population (N = 930) across both treatment groups had a median age of 71 years (range 47 to 97 years). The ethnic/racial distribution was 68% White, 21% Asian, 4.9% Black, and 5% other. Disease stage was distributed as follows: 32% metastatic (M1), 31% locally advanced (T3/4 NX M0 or any T N1 M0), 28% localized (T1 or T2 N0 M0), and 10% not classifiable.

The primary efficacy results of Orgovyx to leuprorelin on achieving and maintaining serum testosterone at castrate levels (T< 50 ng/dL) are shown in Table 3 and Figure 1. The baseline testosterone levels and the time-course of testosterone suppression by Orgovyx and leuprorelin during the 48 week treatment period are shown in Figure 2.

Table 3. Medical castration rates (testosterone concentrations < 50 ng/dL) from week 5 day 1 (day 29) through week 49 day 1 (day 337) in HERO

	Orgovyx 360/120 mg	**Leuprorelin 22.5 or 11.5 mg[a]**
No. treated	622[b]	308[b]
Responder rate (95% CI)[c]	96.7% (94.9%, 97.9%)	88.8% (84.6%, 91.8%)
Difference from leuprorelin (95% CI)	7.9% (4.1%, 11.8%)[d] p-value < 0.0001	

[a] 22.5 mg dosed in Europe and North America; 11.25 mg dosed in Asia. The castration rate of the subgroup of patients receiving 22.5 mg leuprorelin (n = 264) was 88.0% (95% CI: 83.4%, 91.4%).

[b] Two patients in each arm did not receive the study treatment and were not included.
[c] Kaplan-Meier estimates within group.
[d] Non-inferiority was tested with a margin of -10%.

Figure 1: Cumulative incidence of testosterone concentrations < 50 ng/dL in HERO

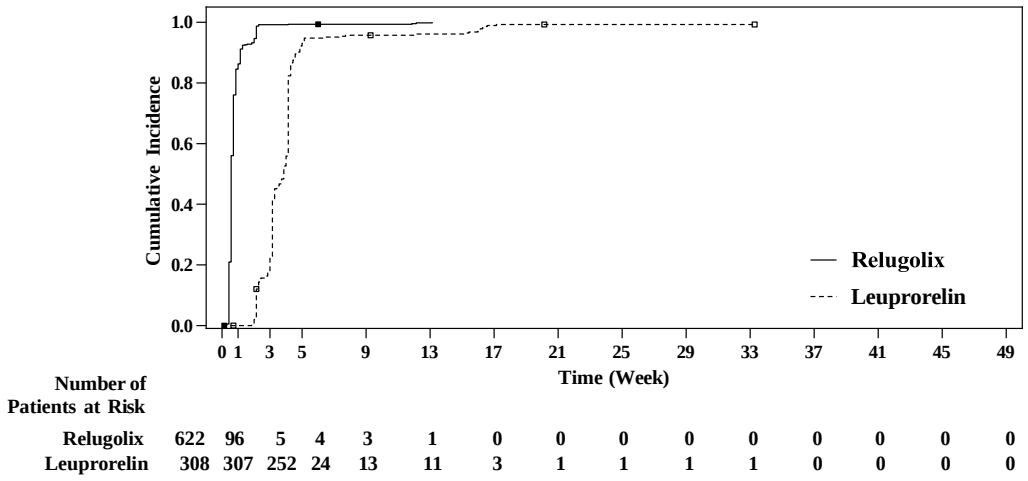
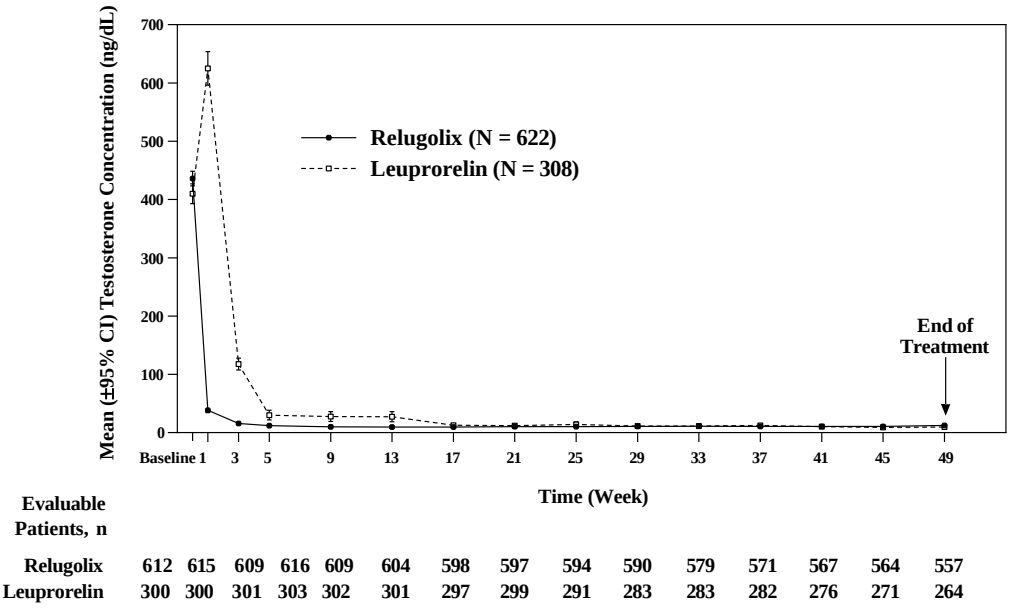


Figure 2: Testosterone concentrations from baseline to week 49 (mean and 95% CI) in HERO



A summary of the results of the key secondary endpoints are shown in Table 4.

Table 4. Summary of key secondary endpoints

Secondary endpoint	Orgovyx (N = 622)	Leuprorelin (N = 308)	p-Value
Cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on day 4	56.0	0.0	<0.0001
Cumulative probability of testosterone suppression to < 50 ng/dL prior to dosing on day 15	98.7	12.1	<0.0001
Proportion of patients with PSA response at Day 15 followed with confirmation at day 29	79.4	19.8	<0.0001

Cumulative probability of testosterone suppression to < 20 ng/dL prior to dosing on day 15	78.4	1.0	<0.0001

Abbreviations: PSA = prostate-specific antigen.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Orgovyx in all subsets of the paediatric population in treatment of advanced hormone-sensitive prostate cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

After oral administration of a single 360 mg loading dose, the mean (± standard deviation [± SD]) of AUC_{0-24} and C_{max} of relugolix were 985 (± 742) ng.hr/mL and 215 (± 184) ng/mL, respectively. After administration of a 120 mg dose once daily, the mean (± SD), C_{max}, C_{avg} (average plasma concentration over the 24-hour dosing interval), and C_{trough} of relugolix at steady-state were 70 (± 65) ng/mL, 17.0 (± 7) ng/mL and 10.7 (± 4) ng/mL, respectively.

The accumulation of exposure to relugolix upon once daily administration of a 120-mg dose of relugolix is approximately 2-fold. After once daily administration of relugolix following a 360-mg loading dose on the first day of administration, steady state of relugolix is achieved by day 7.

Absorption

The absorption of relugolix after oral administration is primarily mediated by intestinal P-gp, for which relugolix is a substrate. After oral administration, relugolix is rapidly absorbed, reaching quantifiable concentration by 0.5 hours post-dose followed by one or more subsequent absorption peaks. The median (range) time to C_{max} (t_{max}) of relugolix is 2.25 hours (0.5 to 5.0 hours). The absolute bioavailability of relugolix is 11.6%.

After administration of a single 120-mg dose of relugolix following consumption of a high-calorie, high-fat meal (approximately 800 to 1 000 calories with 500, 220, and 124 from fat, carbohydrate, and protein, respectively), the $AUC_{0-\infty}$ and C_{max} were decreased 19% and 21%, respectively. The decreases in exposure to relugolix with food are not considered to be clinically meaningful and therefore Orgovyx may be administered without regard to food (see section 4.2).

Distribution

Relugolix is 68 to 71% bound to plasma proteins, primarily to albumin and to a lesser extent to α_1-acid glycoprotein. The mean blood-to-plasma ratio is 0.78. Based on the apparent volume of distribution (Vz), relugolix distributes widely to tissues. The estimated volume of distribution at steady state (Vss) is 3 900 L.

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.

Elimination

Once absorbed, approximately 19% of relugolix is eliminated as unchanged active substance in the urine and approximately 80% is eliminated through multiple biotransformation pathways, including CYP3A and CYP2C8 and multiple other minor metabolic pathways, with a minor contribution from biliary secretion of unchanged medicinal product and/or metabolites. 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 drug.

Linearity/non-linearity

Relugolix is associated with greater than dose-proportional increases in exposure at doses below approximately 80 mg, which is consistent with the dose-dependent saturation of intestinal P-gp and the corresponding decreasing contribution of intestinal P-gp efflux to the oral bioavailability of relugolix as the dose is increased. Upon saturation of intestinal P-gp, a greater proportion of the absorption of relugolix is governed by passive diffusion, and the exposure to relugolix increases in proportion to dose within the 80- to 360-mg dose range. The saturation of intestinal P-gp with higher doses of relugolix is demonstrated by the dose-related increases in exposure to relugolix associated with erythromycin, a strong P-gp inhibitor (and moderate CYP3A inhibitor), where the increases in exposure was less for a 120-mg dose compared with lower doses of relugolix (20 or 40 mg) (see section 4.5).

Special populations

Population PK (PopPK) and PopPK/PD analyses suggest that there are no clinically meaningful differences in exposure of relugolix or testosterone concentrations based on age, race or ethnicity, body size (body weight or body mass index) or stage of cancer.

Renal impairment
Based upon the dedicated renal impairment studies with 40 mg relugolix, the exposure to relugolix (AUC_{0-t}) was increased by 1.5-fold in patients with moderate renal impairment and by up to 2.0-fold in patients with severe renal impairment as compared to subjects with normal renal function. The increases in patients with moderate renal impairment are not considered to be clinically meaningful. With respect to patients with severe renal impairment, caution is warranted upon once daily administration of a 120-mg dose of relugolix (see section 4.4).

The effect of end stage renal disease with or without haemodialysis on the pharmacokinetics of relugolix has not been evaluated. The amount of relugolix removed by haemodialysis is unknown.

Hepatic impairment
After administration of a single 40-mg dose of relugolix to patients with mild or moderate hepatic impairment, the total exposure to relugolix ($AUC_{0-\infty}$) was decreased by 31% or was comparable, respectively, compared to subjects with normal hepatic function. The mean elimination half-life of relugolix in patients with mild or moderate hepatic impairment and healthy control subjects was comparable.

No dose adjustment for Orgovyx in patients with mild or moderate hepatic impairment is required (see section 4.2). The effects of severe hepatic impairment on the pharmacokinetics of relugolix have not been evaluated.

5.3 Preclinical safety data

Non-clinical data based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential reveal no special hazard for humans beyond those discussed below.

In human GnRH-receptor knock-in male mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses ≥ 3 mg/kg twice daily for 28 days. The effects of relugolix were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal. These effects in knock-in male mice are likely associated with the pharmacodynamics of relugolix; however, the relevance of these findings to humans is unknown. In a 39-week repeat dose toxicity study in monkeys, there were no significant effects on male reproductive organs at oral relugolix doses

up to 50 mg/kg/day (approximately 36 times the human exposure at the recommended dose of 120 mg daily based on AUC). Relugolix (doses of ≥ 1 mg/kg) suppressed LH concentrations in castrated male cynomolgus monkeys; however, the suppressive effect of relugolix on LH and sex hormones was not evaluated in the 39-week toxicity study in intact monkeys. Therefore, the relevance of the lack of effect on reproductive organs in intact male monkeys to humans is unknown.

In pregnant rabbits orally dosed with relugolix during the period of organogenesis, spontaneous abortion and total litter loss were observed at exposure levels (AUC) less than that achieved at the recommended human dose of 120 mg/day. No effects on embryofoetal development were observed in rats; however, relugolix does not interact significantly with GnRH receptors in that species.

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 studies have shown that relugolix may pose a risk for the aquatic compartment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium starch glycolate (E468)
Hydroxypropyl cellulose (E463)
Magnesium stearate (E572)
Hypromellose (E464)
Titanium dioxide (E171)
Iron oxide red (E172)
Carnauba wax (E903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Orgovyx film-coated tablets are supplied in a bottle. Each high-density polyethylene (HDPE) bottle contains 30 film-coated tablets and a desiccant and is closed with a child-resistant induction seal polypropylene (PP) cap.
Pack sizes of 30 and 90 (3 packs of 30) film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona,
Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1642/001
EU/1/22/1642/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29 April 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

Legal category: POM (Prescription-only medicine)
Date of preparation: April 2024
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