SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Orgovyx® 120 mg film-coated tablets

Relugolix 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

Relugolix is indicated:

-For the treatment of adult patients with advanced hormone-sensitive prostate cancer.

-For the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy.

-As neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer.

4.2 Posology and method of administration

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

Posology

Treatment with relugolix 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.

Relugolix may be used as neo-adjuvant or adjuvant therapy prior to or in combination with radiotherapy in high-risk localised and locally advanced prostate cancer.

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 relugolix with oral P-glycoprotein (P-gp) inhibitors is not recommended. If co-administration is required, relugolix should be taken first, and dosing should be separated by at least 6 hours (see section 4.5). Treatment with this medicine 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 relugolix with combined P-gp and strong cytochrome P450 (CYP) 3A inducers is not recommended. If co-administration is required, the dose 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 relugolix once daily, must be resumed (see section 4.5).

Missed doses

If a dose is missed, it 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 relugolix is interrupted for greater than 7 days, it 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 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. This medicine 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 this medicine.

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 relugolix 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
Clinical interaction studies with P-gp inhibitors (erythromycin and azithromycin) and combined P-gp and strong CYP3A4 inducers (rifampicin) have shown to affect the exposure of relugolix to a clinically relevant extent. Effect of co-administration on the exposure to relugolix and associated dosing recommendations are summarised in Table 1. This list also includes expected effect and recommendations with other potentially interacting medicinal products.

P-gp inhibitors
Co-administration of relugolix with oral P-gp inhibitors is not recommended. Relugolix is a P-gp substrate (see section 5.2).

If co-administration with once or twice daily oral P-gp inhibitors is required (e.g. azithromycin), this medicine 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 relugolix 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 is interrupted for more than 7 days, resume administration of this medicine 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 relugolix with combined P-gp and strong CYP3A inducers is not recommended.
If co-administration is required, the relugolix dose should be increased (see section 4.2). After discontinuation of the combined P-gp and strong CYP3A inducer, the recommended dose of this medicine should be resumed once daily.

Other medicinal products
No clinically significant differences in the pharmacokinetics of relugolix were observed upon co-administration with acid reducing agents.
Since androgen deprivation treatment may prolong the QT interval, the concomitant use 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).

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

Interacting drug dose regimen	Relugolix dose regimen	Change in relugolix $AUC_{0\text{-}inf}$	Change in relugolix C_{max}	Recommendation
Medicinal products that are oral P gp inhibitors				
erythromycin 500 mg QID, multiple doses (P-gp and moderate CYP3A4 inhibitor)	120 mg single dose	3.5 -fold ↑	2.9 -fold ↑	Concomitant use of Orgovyx with erythromycin, azithromycin and other oral P-gp inhibitors is not recommended If concomitant use with once or twice daily oral P-gp inhibitors is required (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 (P-gp inhibitor)	120 mg single dose	*1.5 -fold ↑	*1.6 -fold ↑	
azithromycin 500 mg single dose 6 hours after administration of relugolix (P-gp inhibitor)		1.4 -fold ↑	1.3 -fold ↑	
Other medicinal products that are P-gp inhibitor include (but not limited to): <u>*Anti infectives*</u> azithromycin, erythromycin, clarithromycin, gentamicin, tetracycline. <u>*Antifungal agents*</u> ketoconazole, itraconazole. <u>*Antihypertensives*</u> carvedilol, verapamil. <u>*Antiarrhythmics*</u> amiodarone, dronedarone, propafenone,	Therapeutic dose for Orgovyx	Expected: ↑ See also clinical study results with erythromycin and azithromycin (above).	Expected: ↑ See also clinical study results with erythromycin and azithromycin (above).	

quinidine. *Antianginal agents* ranolazine *Immunosupressive agents* cyclosporine. *HIV or HCV protease inhibitors* ritonavir, telaprevir.				
Medicinal products that are CYP3A4 inhibitors				
voriconazole 200 mg BD, multiple doses (strong CYP3A4 inhibitor)	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 OD, multiple doses (moderate CYP3A4 inhibitor)	40 mg single dose	19%↑	44% ↑	
atorvastatin 80 mg OD, multiple doses (weak CYP3A4 inhibitor)	40 mg single dose	5%↓	22%↓	
Medicinal products that are combined P gp and strong CYP3A4 inducers				
rifampicin 600 mg OD, multiple doses	40 mg single dose	55%↓	23%↓	Co-administration of Orgovyx with rifampicin and other strong CYP3A4 and P-gp inducers is not recommended, as this may decrease the AUC and C_{max} of relugolix and may therefore reduce the therapeutic effects of Orgovyx. An increased dose is

				recommended if co-administration is required (see section 4.2).
Medicinal products that are combined P gp and strong CYP3A4 inducers include (but not limited to): <u>*Androgen receptor inhibitor*</u> apalutamide. <u>*Anticonvulsants*</u> carbamazepine, phenytoin, phenobarbital. <u>*Anti infectives*</u> rifampicin, rifabutin. <u>*Medicinal herb*</u> St. John's Wort (Hypericum perforatum). <u>*HIV or HCV protease inhibitors*</u> Ritonavir. <u>*Non nucleoside reverse transcriptase inhibitors*</u> efavirenz.	Therapeutic dose for Orgovyx	Expected: ↓ See also clinical study results with erythromycin and azithromycin (above).	Expected: ↓ See also clinical study results with erythromycin and azithromycin (above).	
Combination with other medicines for advanced hormone-sensitive prostate cancer				
Abiraterone (not an inhibitor/inducer of CYP3A4 and/or P-gp)	Therapeutic dose for Orgovyx	Expected: ↔	Expected: ↔	Abiraterone and docetaxel are not known inhibitors/inducers of enzymes and transporters contributing to the metabolism and transport of relugolix. No clinically meaningful interaction is expected and no dose
Docetaxel (not an inhibitor/inducer of CYP3A4 and/or P-gp)	Therapeutic dose for Orgovyx	Expected: ↔	Expected: ↔	

				adjustment of Orgovyx is required.
Darolutamide (weak inducer of CYP3A4)	Therapeutic dose for Orgovyx	Expected: ↔	Expected: ↔	Darolutamide is a weak inducer of CYP3A4. However the potential decrease in exposure is not expected to be clinically meaningful. No dose adjustment of Orgovyx is required.
Enzalutamide (strong CYP3A4 inducer and P-gp inhibitor)	Therapeutic dose for Orgovyx	Expected: ↔	Expected: ↔	Enzalutamide may decrease (CYP3A4 induction) and/or increase (P-gp inhibition) the relugolix exposure. Based on limited data (n=20) in men who received a 120 mg dose of relugolix and 80 to 160 mg doses of enzalutamide concomitantly for up to 266 days in the phase 3 study, plasma relugolix trough concentrations did not change to a clinically significant extent upon adding enzalutamide to the relugolix monotherapy. Therefore, no dose modifications are recommended for co-administration of relugolix and enzalutamide.
Apalutamide (P-gp and strong CYP3A4 inducer)	Therapeutic dose for Orgovyx	Expected: ↓	Expected: ↓	In a clinical study, Orgovyx 120 OD (without apalutamide) and Orgovyx 240 OD (with 240 OD apalutamide) resulted in similar C_{trough}

				values. An increased dose of Orgovyx is recommended if co-administration with apalutamide is required (see section 4.2). Stable plasma concentrations for relugolix, apalutamide and its metabolite, N-desmethylapalutamide were demonstrated over a 12-week period in 24 men when relugolix (240 mg once a day) was coadministered with apalutamide.

Abbreviations: **OD**: once a day, **BD**: twice a day, **QID**: four times a day, **HIV**: human immunodeficiency virus, **HCV**: hepatitis C virus.
*: Upon co-administration of azithromycin and relugolix, relugolix exposure increases up to 5-fold were observed in the first 3 hours after dosing in the median concentration-time curves. After a dose separation window of 6 hours, the increase in relugolix exposure in the median concentration-time curves was maximally 1.6-fold in the first 3 hours after dosing.

Potential for relugolix to affect the exposure to other medicinal products
Relugolix is a weak inducer of CYP3A mediated metabolism, and an inhibitor of BCRP and P-gp in vitro. Effect of co-administration of relugolix on the exposure of midazolam, rosuvastatin and dabigatran and associated dosing recommendations are summarised in Table 2. This list also includes expected potential interacting effect of relugolix on other medicinal products.

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.

Table 2. Effect of relugolix on exposure (C_{max}, AUC_{0-inf}) of co-administered medicinal products and recommendations

Relugolix dose regimen	Drug dose regimen	Change in drug AUC_{0-inf}	Change in drug C_{max}	Recommendation
Medicinal products that are CYP3A substrates				
120 mg OD, multiple doses	Midazolam 5mg single dose (sensitive CYP3A substrate)	22% ↓	14% ↓	No dose adjustment of midazolam and other CYP3A substrates is required. Clinically meaningful interactions with other CYP3A substrates than midazolam are not expected. If a decrease in the therapeutic effects occur, medicinal products (e.g. statins) may be titrated to achieve desired therapeutic effects
Medicinal products that are BCRP substrates				
120 mg OD, multiple doses	Rosuvastatin 10mg single dose (sensitive BCRP and OATP1B1 substrate)	27% ↓	34% ↓	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.
Medicinal products that are P-gp substrates				

120mg single dose	Dabigatran exetilate 150mg single dose (P-gp substrate)	17% ↑	18% ↑	The increase in dabigatran exposure is not considered to be clinically meaningful. Therefore, clinically meaningful effects of a 120 mg dose of 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.
Combination with other medicines for advanced hormone-sensitive prostate cancer				
Therapeutic dose for Orgovyx	Abiraterone (CYP3A4 substrate)	Expected: ↔	Expected: ↔	No clinically meaningful changes in exposure are expected and no dose adjustments are necessary for abiraterone, enzalutamide, apalutamide, darolutamide or docetaxel when co-administered with relugolix.
Therapeutic dose for Orgovyx	Docetaxel (CYP3A substrate)	Expected: ↔	Expected: ↔	
Therapeutic dose for Orgovyx	Darolutamide (CYP3A, P-gp and BCRP substrate)	Expected: ↔	Expected: ↔	
Therapeutic dose for Orgovyx	Enzalutamide (CYP2C8 and CYP3A4 substrate)	Expected: ↔	Expected: ↔	
Therapeutic dose for Orgovyx	Apalutamide (CYP2C8 and CYP3A4 substrate)	Expected: ↔	Expected: ↔	

Abbreviations: OD: once a day

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 must be used, during treatment and for up to 2 weeks after the last dose of this medicine.

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 is 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, this medicine may impair fertility in males of reproductive potential (see section 5.3).

4.7 Effects on ability to drive and use machines

This medicine 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 1 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 3. 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	
Uncommon	Myocardial infarction[g]
Unknown	QT prolonged (see sections 4.4 and 4.5)
Vascular disorders	
Very common	Hot flush
Common	Hypertension
Gastrointestinal disorders	
Very common	Diarrhoea[b]
	Constipation
Common	Nausea
Skin and subcutaneous tissue disorders	
Common	Hyperhidrosis
	Rash
Uncommon	Urticaria
	Angioedema
Musculoskeletal and connective tissue disorders	
Very common	Musculoskeletal pain[c]
Uncommon	Osteoporosis/osteopenia
Reproductive and breast disorders	
Common	Libido decreased
General disorder and administration site conditions	
Very common	Fatigue[d]
Investigations	
Common	Weight increased
	Glucose increased[e]
	Triglyceride increased[d]
	Blood cholesterol increased[f]
Uncommon	Aspartate aminotransferase increased
	Alanine aminotransferase increased[e]

a Includes libido decreased and loss of libido
b Includes diarrhoea and colitis
c 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
d Includes fatigue and asthenia

e Grade 3/4 increases identified through clinical laboratory test monitoring (see below)
f There were no reported cholesterol increases > grade 2
g Includes myocardial infarction and acute myocardial infarction

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 relugolix 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 relugolix. 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 relugolix, 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 relugolix, 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.

After 48-weeks of treatment in the HERO study, the incidence of MACE was 2.9% (18 of 622 patients) in the relugolix group and 6.2% (19 of 308 patients) in the leuprolide group.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no known specific antidote for overdose. In the event of an overdose, this medicine 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 relugolix 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 relugolix was evaluated in HERO, a randomised, open-label study in adult men with androgen-sensitive advanced prostate cancer requiring at least one 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 localised 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 2). 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 3).

In the primary analysis, a total of 934 patients were randomised to receive relugolix or leuprorelin in a 2:1 ratio for 48 weeks:

a) Relugolix 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.

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% localised (T1 or T2 N0 M0), and 10% not classifiable.

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

Table 4. Medical castration rates (testosterone concentrations < 50 ng/dL) from week 5 day 1 (day 29) through week 49 day 1 (day 337) in HERO

	Relugolix 360/120 mg	Leuprorelin 22.5 or 11.25 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

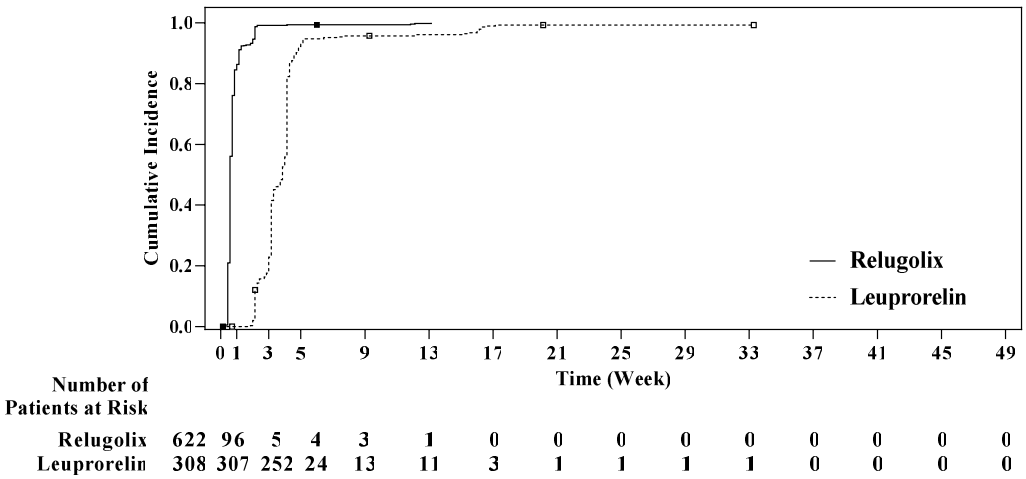
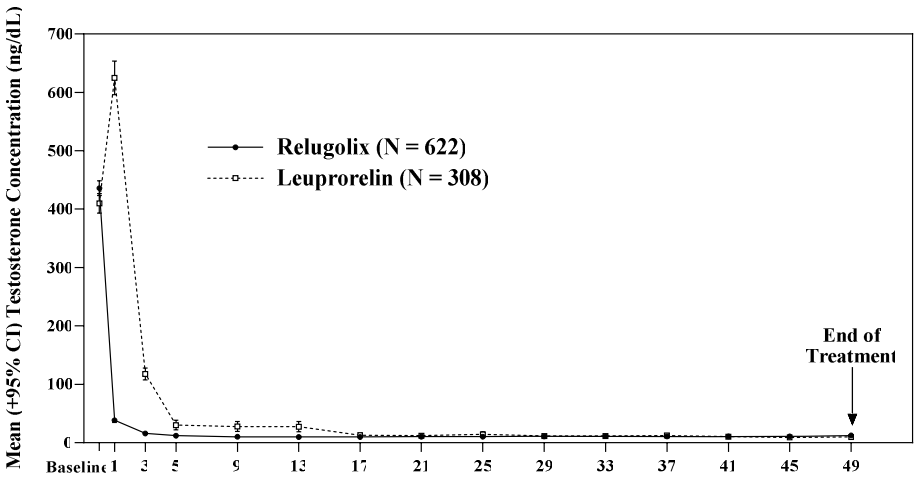


Figure 2: Testosterone concentrations from baseline to week 49 (mean and 95% CI) in HERO



Evaluable Patients, n															
Relugolix	612	615	609	616	609	604	598	597	594	590	579	571	567	564	557
Leuprorelin	300	300	301	303	302	301	297	299	291	283	283	282	276	271	264

A summary of the results of the key secondary endpoints are shown in Table 3.

Table 5. Summary of key secondary endpoints

Secondary endpoint	Relugolix (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.

Combination with radiotherapy

The effect of relugolix in combination with radiotherapy is based on an indirect comparison to the LHRH receptor agonists and antagonists efficacy data by using the main clinical efficacy surrogate endpoint (testosterone suppression) demonstrating non-inferiority to LHRH agonists and indirectly establish efficacy. In patients with locally advanced prostate cancer several randomised long-term clinical trials provide evidence for the benefit of androgen deprivation therapy (ADT) in combination with radiotherapy (RT) compared to RT alone (RTOG 85-31, RTOG 86-10, EORTC 22863). Clinical data from a phase III clinical trial (EORTC 22961) in 970 patients with locally advanced prostate cancer (mainly T2c-T4 with some T1c to T2b patients with pathological regional nodal disease) have shown that radiotherapy followed by long-term therapy (3 years) is preferable to short-term therapy (6 months). Overall total mortality at 5 years in the short-term hormonal treatment and long-term

hormonal treatment groups was 19.0% and 15.2% respectively, with a relative risk of 1.42 (an upper one sided 95.71% CI = 1.79; or two sided 95.71% CI = [1.09; 1.85], p = 0.65 for non-inferiority and p = 0.0082 for post-hoc test of difference between groups of treatment). The 5-year mortality specifically related to the prostate cancer in the short-term hormonal treatment and long-term hormonal treatment groups was 4.78% and 3.2% respectively, with a relative risk of 1.71 (95% CI = [1.14 to 2.57], p = 0.002). The recommended duration of androgen deprivation therapy in medical guidelines for T3-T4 patients receiving radiotherapy is 2-3 years. Evidence for the indication of high-risk localised prostate cancer is based on a number of published studies of radiotherapy combined with GnRH analogues. Clinical data from five published studies were analysed (EORTC 22863, RTOG 85-31, RTOG 92-02, RTOG 86-10 and D'Amico et al., JAMA 2004), which all demonstrate a benefit for the combination of GnRH analogue with radiotherapy. Clear difference of the respective study populations for the indications locally advanced prostate cancer and high-risk localised prostate cancer was not possible in the published studies.

Paediatric population

The licensing authority has waived the obligation to submit the results of studies with relugolix 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 AUC0-24 and Cmax 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), Cmax, Cavg (average plasma concentration over the 24-hour dosing interval), and Ctrough 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 Cmax (tmax) 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 AUC0-∞ and Cmax were decreased 19% and 21%, respectively. The decreases in exposure to relugolix with food are not considered to be clinically meaningful and therefore it 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 α1 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 (AUC0-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 (AUC0-∞) 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 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

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

This medicine is supplied in a bottle. Each high-density polyethylene (HDPE) bottle contains 30, 33, 90 or 95 film coated tablets and a desiccant and is closed with a child-resistant induction seal polypropylene (PP) cap.

Pack sizes of 30, 33, 90 (3 packs of 30 or 1 pack of 90) and 95 film-coated tablets.

This medicine is also supplied in Alu/Alu blisters containing 30 and 90 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00142/1272

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/06/2022

10 DATE OF REVISION OF THE TEXT

24/03/2026