Drug Monograph

A - Drug Name

relugolix

COMMON TRADE NAME(S): Orgovyx®

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B - Mechanism of Action and Pharmacokinetics

Relugolix is a nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist that inhibits pituitary release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), thereby suppressing testosterone production from the testes. The reduction in testosterone concentrations to below physiologic levels inhibits the proliferation of hormone-dependent prostate cancer cells.

Absorption	Bioavailability	~12%
	Effects with food	No clinically meaningful effect on exposure when given with food. AUC and C_{max} were reduced by 19% and 21%, respectively, following a high-fat, high-calorie meal.
	Time to reach steady state	7 days (including loading dose on day 1)
	Peak plasma levels	~2 hours
Distribution	Distributed widely to tissues	
	PPB	68-71%, mainly to albumin, and α1-acid glycoprotein to a lesser extent

Metabolism	Relugolix is mainly metabolized by CYP3A, with a lesser contribution from CYP2C8 *in vitro*.	
Elimination	Half-life	25 hours (effective)
		61 hours (terminal)
	Feces	81% (4% unchanged)
	Urine	4% (2% unchanged)

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C - Indications and Status

Health Canada Approvals:

- Prostate cancer

Refer to the product monograph for a full list and details of approved indications

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D - Adverse Effects

Emetogenic Potential: Not applicable

The following table lists adverse effects that occurred in patients with advanced prostate cancer treated with relugolix versus leuprolide in a single-agent phase III study. It also includes severe, life-threatening and post-marketing adverse effects from other sources.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arrhythmia (<1%)	E
	Arterial thromboembolism (3%)	E D
	Atrioventricular block (<1%)	E
	Heart failure (<1%)	E D

	Hypertension (8%)	E
	QT interval prolonged (5%) (2% severe)	E D
Dermatological	Hyperhidrosis (<5%)	E
	Rash (<5%) (includes urticaria)	I E
Gastrointestinal	Constipation (12%)	E
	Diarrhea (12%)	E
	Nausea (6%)	E
	Weight gain (8%)	E
General	Fatigue (26%)	E
Hematological	Anemia (<5%)	E
	Hemorrhage (<1%)	E
Hypersensitivity	Angioedema (rare)	I E
Musculoskeletal	Fracture (<1%)	D L
	Musculoskeletal pain (30%)	E
Nervous System	Depression (<5%)	E D
	Dizziness (6%)	E
	Headache (6%)	E
	Insomnia (7%)	E
Renal	Acute kidney injury (<1%)	E
Reproductive and breast disorders	Gynecomastia (<5%)	E D
	↓ Libido (<5%)	E
Vascular	Hot flashes (54%)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for relugolix include hot flashes, musculoskeletal pain, fatigue, constipation, and diarrhea.

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E - Dosing

Refer to protocol by which the patient is being treated.

Correct potassium, calcium, and magnesium abnormalities prior to initiation.

Adults:

Oral:

- Loading dose: 360 mg on day 1
- Maintenance dose: 120 mg daily, starting on day 2

Coadministration with an anti-androgen is not necessary since relugolix does not cause a testosterone surge and the associated clinical flare.

If relugolix is interrupted for > 7 days, restart treatment with a loading dose of 360 mg on day 1, followed by 120 mg daily thereafter.

Dose adjustment for drug-drug interactions:
Refer to Interactions section for dosing recommendations when co-administering with **P-gp inhibitors** or **combined P-gp and strong CYP3A inducers.**

Dosage with Toxicity:

There are no dose reductions for relugolix. Doses may be held for up to 10 days for evaluation and treatment of adverse effects, if required. (Shore et al)

If doses are held for >7 days, restart with a loading dose as outlined above.

Dosage with Hepatic Impairment:

Hepatic Impairment	Relugolix Dose
Mild (Child-Pugh A)	No dose adjustment required.
Moderate (Child-Pugh B)	
Severe (Child-Pugh C)	No data available.

Dosage with Renal Impairment:

Creatinine Clearance (mL/min)	Relugolix Dose
≥ 15	No dose adjustment required.
< 15 Or end-stage renal disease, with or without hemodialysis	No data available.

Dosage in the elderly:

No dose adjustment in patients ≥ 65 years of age is required. There were no overall differences in safety or effectiveness of relugolix when compared to younger patients. Age had no clinically relevant impact on the pharmacokinetics of relugolix or testosterone response in patients aged 45 to 91 years.

Dosage based on ethnicity:

No clinically meaningful effects on relugolix exposure were observed based on race or ethnicity.

Children:

The safety and effectiveness of relugolix in patients aged < 18 years have not been established.

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F - Administration Guidelines

- Administer relugolix with or without food.
- Tablets should be swallowed whole and not crushed or chewed.
- If a dose is missed, administer the dose as soon as possible within 12 hours of missed dose. If the dose is missed by more than 12 hours, skip the dose and administer the next dose at the next planned time. Do not give extra tablets to make up for the missed dose.
- If doses are held for >7 days, restart with a loading dose as outlined in the Dosing section.
- Store between 15°C to 30°C in the original container.

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G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- Androgen deprivation therapy can prolong the QT interval. Consider the risks versus benefits of using relugolix in patients who have risk factors for QTc prolongation and torsade de pointes.
- Long-term suppression of testosterone is associated with decreased bone density, which may increase the risk of osteoporosis and bone fractures.

Other Drug Properties:

- Carcinogenicity: No

Pregnancy and Lactation:

- Mutagenicity: No
- Clastogenicity: No
- Embryotoxicity: Documented in animals
- Fetotoxicity: Documented in animals
- Teratogenicity: Documented in animals
- Abortifacient effects: Documented in animals
- Pregnancy:
  Relugolix is **only indicated in patients with prostate cancer**. Adequate contraception should be used by patients and their partners during treatment, and for at least **2 weeks** after the last dose.
- Excretion into breast milk: Documented in animals
- Breastfeeding:
  Relugolix is **only indicated in patients with prostate cancer**. There are no data on the presence of relugolix or its metabolites in human milk, on the effects of the breastfed child or milk production.
- Fertility effects: Probable
  Documented in studies in male animals

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H - Interactions

In vitro, relugolix is a(n):

- substrate of CYP3A and CYP2C8
- inducer of CYP3A4 and CYP2B6
- substrate of P-gp
- inhibitor of BCRP and P-gp (clinical significance not established)

No clinically meaningful differences in relugolix pharmacokinetics were observed when co-administered with voriconazole, a strong CYP3A inhibitor.

Relugolix suppresses the pituitary gonadal system, which may affect diagnostic test results of pituitary gonadotropic and gonadal functions conducted during and after treatment.

AGENT	EFFECT	MECHANISM	MANAGEMENT
Oral P-glycoprotein inhibitors	↑ relugolix concentration and/or toxicity (e.g. erythromycin ↑ relugolix exposure by 3.5-fold)	Relugolix is a P-gp substrate	Avoid co-administration. If must co-administer, give relugolix first and separate dosing by at least 6 hours; monitor closely for toxicity. Or hold relugolix for up to 2 weeks if a short

			course of treatment with a P-gp inhibitor is required. If doses are held for >7 days, restart with a loading dose as outlined in the Dosing section.
Combined P-gp and strong CYP3A inducers (i.e. rifampin)	↓ relugolix concentration and/or efficacy (e.g. rifampin ↓ relugolix exposure by 55%)	Relugolix is a P-gp and CYP3A substrate	Avoid co-administration. If must co-administer, ↑ relugolix dose to 240 mg daily. Resume the 120 mg daily dose after discontinuation of the combined P-gp and strong CYP3A inducer.
Medications that may prolong QT (i.e. amiodarone, procainamide, sotalol, venlafaxine, amitriptyline, sunitinib, methadone, chloroquine, clarithromycin, haloperidol, fluconazole, moxifloxacin, domperidone, ondansetron)	↑ risk of QT prolongation	Additive effects	Avoid co-administration.
Medications that can affect electrolyte levels (i.e. thiazide and related diuretics, laxatives and enemas, amphotericin B, high-dose corticosteroids, and proton pump inhibitors)	↑ risk of QT prolongation	Electrolyte disturbances can ↑ risk of QT prolongation	Caution with concomitant use.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and as clinically indicated
Liver function tests	Baseline and as clinically indicated
Renal function tests	Baseline and as clinically indicated
ECG and serum electrolyte levels (potassium, calcium, and magnesium)	Baseline, at each visit, and as clinically indicated (more frequently in patients with electrolyte abnormality or at risk of QT prolongation)
Prostate specific antigen (PSA)	Baseline and as clinically indicated
Testosterone serum concentration	Baseline and as clinically indicated if PSA increases
Clinical toxicity assessment for hot flashes, musculoskeletal pain, fatigue, GI effects, fractures/ osteoporosis	Baseline and as clinically indicated

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

ODB - General Benefit (ODB Formulary)

- relugolix

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K - References

NCI drug dictionary: relugolix. Accessed February 28, 2025.

Prescribing Information: Orgovyx® (relugolix). Sumitomo Pharma America, Inc. October 2024

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Shore ND, Saad F, Cookson MS, et al. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer. N Engl J Med. 2020 Jun 4;382(23):2187-2196.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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