DRUG NAME: Relugolix

SYNONYM(S): TAK-385[1]

COMMON TRADE NAME(S): ORGOVYX®

CLASSIFICATION: hormonal agent

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Relugolix is an orally administered nonpeptide gonadotropin-releasing hormone (GnRH) receptor antagonist (also known as luteinizing hormone-releasing hormone [LHRH] antagonist). It competitively binds to pituitary GnRH receptors, reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the systemic circulation, which consequently decreases testosterone production by the testes. Relugolix induces testosterone suppression without an initial testosterone surge or clinical flare; therefore, coadministration with an anti-androgen is not required. Medical castration levels are achieved in 56% of patients by day 4 and 99% by day 15.[2]

PHARMACOKINETICS:

Oral Absorption	T_{max}= 2.25 h (range 0.5-5 h); bioavailability = approximately 12%; food has no clinically meaningful effect on pharmacokinetics	
Distribution	widely distributed to tissues	
	cross blood brain barrier?	no information found
	volume of distribution	3900 L at steady state
	plasma protein binding	68-71%; primarily bound to albumin
Metabolism	primarily by CYP3A and to a lesser extent by CYP2C8 (*in vitro)*	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	primarily by fecal elimination	
	urine	4% (2.2% unchanged)
	feces	81% (4.2% unchanged)
	terminal half life	mean terminal elimination half-life: 61 h (mean effective half-life: 25 h)
	clearance	mean total clearance: 29 L/h
Elderly	no clinically significant difference	
Ethnicity	no clinically significant difference	

Adapted from standard reference[1,2] unless specified otherwise.

USES:

Primary uses:

*Prostate Cancer

Other uses:

*Health Canada approved indication

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SPECIAL PRECAUTIONS:

Caution:
- risk of ***QTc prolongation*** is increased in patients with congenital long QT syndrome, history of QT prolongation, or those taking medications known to prolong QTc interval; monitor ECG and correct electrolyte abnormalities prior to treatment as indicated[2]
- relugolix ***dose modification*** may be required if used concurrently with a ***combined P-gp and strong CYP 3A inducer***[2]

Carcinogenicity: In animal studies, relugolix was not carcinogenic at exposures approximately 50-150 times higher than those seen following human clinical exposure.[2]

Mutagenicity: Not mutagenic in Ames test. Relugolix was not clastogenic in the mammalian *in vivo* and *in vitro* chromosome tests.[2]

Fertility: In animal studies, test results varied based on test species. In mice, male test subjects showed reduced organ weights for the prostate, seminal vesicles, and testes at low doses and some effects were not fully reversible during the study period. In monkeys, no significant effects on male reproductive organs were observed at exposures approximately 36 times higher than those seen following human clinical exposure. Based on findings from animal studies and its mechanism of action, the manufacturer states that relugolix may impair fertility in male patients of reproductive potential.[2]

Pregnancy: Animal studies have shown that exposure to relugolix in early pregnancy may increase risk of pregnancy loss. Spontaneous abortion, embryo-fetal lethality, and total litter loss were observed in animal studies at exposures less than those seen following expected human exposure at clinical doses. It is not known whether relugolix or its metabolites are present in semen. Barrier protection (e.g., condom) is recommended for vaginal intercourse with a pregnant woman. In male patients with female partners of childbearing potential, contraception is recommended during treatment and for at least 2 weeks after the last dose.[2,3]

Breastfeeding: is not recommended due to the potential secretion into breast milk. In animal studies, relugolix was detected in the milk of lactating test subjects.[2]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.[4,5]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	anemia (<5%)
cardiac (see paragraph following **Side Effects** table)	***atrioventricular block*** (<1%)
	arrhythmia (<1%)
	cardiac failure (<1%)
	myocardial infarction (severe <1%); fatalities reported
endocrine	decreased gonadal hormone levels; may affect diagnostic test results of pituitary gonadotropic and gonadal function (during and after relugolix treatment)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential:* minimal (rare)[6]
	constipation (12%)
	diarrhea (12%, severe <1%)
	nausea (6%)
	vomiting (2-3%)[7]
general disorders and administration site conditions	fatigue/asthenia (26%, severe <1%)
immune system	***hypersensitivity*** (severe <1%); reactions include severe angioedema, urticaria, and pharyngeal edema
infections and infestations	urinary tract infection (<1%)
	pneumonia (<1%)
injury, poisoning, and procedural complications	fracture (<1%)
investigations	ALT increase (27%, severe <1%)
	AST increase (18%)
	cholesterol increased (2%)
	glucose increase (44%, severe 3%); see paragraph following **Side Effects** table
	hemoglobin decrease (29%, severe <1%)
	QTc prolongation (5%, severe 2%); see paragraph following **Side Effects** table
	triglycerides increase (35%, severe 2%)
metabolism and nutrition	weight gain (8%)
musculoskeletal and connective tissue	arthralgia (12%, severe <1%)[8]
	musculoskeletal pain (30%, severe <1%)
	osteopenia/osteoporosis (<1%)[9]; see paragraph following **Side Effects** table
nervous system	dizziness (6%)
	headache (6%)
psychiatric	***decreased libido*** (<5%); see paragraph following **Side Effects** table
	depression (<5%)
	insomnia (7%)
renal and urinary	acute kidney injury (severe <1%)
reproductive system and breast disorders	***erectile dysfunction***[3,10]; see paragraph following **Side Effects** table
	gynecomastia (<5%)
skin and subcutaneous tissue	hyperhidrosis (<5%)
	rash (<5%)
vascular	***hot flashes*** (54%, severe <1%); see paragraph following **Side Effects** table

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	hemorrhage (<1%)
	hypertension (8%, severe 2%)
	major adverse cardiovascular events (3%, severe <1%); includes stroke, myocardial infarction, and death from any cause; see paragraph following **Side Effects** table

Adapted from standard reference[2,3] unless specified otherwise.

Long-term androgen deprivation therapy has been associated with an increased risk of cardiovascular disease, QT prolongation, decreased bone density, and insulin resistance. The expected physiological effects of testosterone suppression (e.g., hot flashes, decreased libido, and erectile dysfunction) have been reported with relugolix.[1,3,9]

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
acid-reducing agents[2]	no clinically significant effect on relugolix	pH-dependent solubility of relugolix	no action required
apalutamide[11,12]	no clinically significant effect on mean C_{trough} of relugolix[13]; castration levels were maintained with concurrent use	combined induction of P-gp (weak) and CYP 3A4 (strong) by apalutamide	no action required
azithromycin[9]	1.5 to 5-fold increase in relugolix AUC and 1.6-fold increase in C_{max}	inhibition of P-gp by azithromycin	- avoid if possible; relugolix may be held for up to two weeks while taking azithromycin (repeat relugolix loading dose if interrupted more than 7 days) - if concurrent use is unavoidable, give relugolix first and separate azithromycin dosing by at least 6 hours; monitor for relugolix toxicity
erythromycin[2,3]	3 to 6-fold increase in relugolix AUC and 2 to 6-fold increase in C_{max}	combined inhibition of P-gp and CYP 3A (moderate) by erythromycin	- avoid if possible; relugolix may be held for up to two weeks while taking erythromycin (repeat relugolix loading dose if interrupted more than 7 days) - if concurrent use is unavoidable, give relugolix first and separate erythromycin dosing by at least 6 hours; monitor for relugolix toxicity
enzalutamide[9]	no clinically significant effect on relugolix	inhibition of P-gp and induction of CYP 3A (strong) by enzalutamide	no action required

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AGENT	EFFECT	MECHANISM	MANAGEMENT
rifampin[2]	55% decrease in relugolix AUC and 23% decrease in C_{max}	combined induction of P-gp and CYP 3A (strong) by rifampin	avoid if possible; if concurrent use is unavoidable, increase relugolix to 240 mg once daily (after rifampin is discontinued, resume relugolix at the prior dose of 120 mg once daily)
voriconazole[9]	not clinically significant; 12% increase in relugolix AUC and 18% increase in C_{max}	strong inhibition of CYP 3A by voriconazole	no action required

Relugolix is a substrate of P-gp. Coadministration with an oral ***P-gp inhibitor*** may increase the plasma concentration of relugolix. To avoid coadministration, relugolix may be interrupted for up to 2 weeks if a short course of treatment with an oral P-gp inhibitor is required. However, following relugolix treatment interruptions of 7 days or longer, repeat the relugolix loading dose of 360 mg before resuming treatment at 120 mg once daily thereafter. Alternatively, relugolix may be given concurrently with an oral P-gp inhibitor if administration is spaced six hours apart and relugolix is given first. Monitor for relugolix toxicity.[2]

Combined P-gp and strong CYP 3A inducers may decrease the plasma concentration of relugolix. If coadministration with relugolix is unavoidable, consider increasing relugolix dose to 240 mg once daily while the treatments overlap and then resume relugolix dosing at 120 mg once daily when the combined P-gp inhibitor and strong CYP 3A inducer is discontinued.[2]

In vitro, relugolix is a substrate and a weak inducer of CYP 3A, as well as an inhibitor of BCRP and P-gp. No clinically significant interactions with substrates of CYP 3A, P-gp and BCRP are reported.

In vitro, relugolix is a substrate of CYP 2C8 and an inducer of CYP 2B6; clinical significance is unknown.[2]

SUPPLY AND STORAGE:

Oral: Sumitomo Pharma Canada, Inc. supplies relugolix as 120 mg film-coated tablets. Store at room temperature. Store in the original bottle with desiccant.[2]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated.

Adults:

BC Cancer usual dose noted in ***bold, italics***

Oral[2,8]*:*

Loading dose: 360 mg PO on day 1

Maintenance: 120 mg (range 120-240 mg) PO once daily* starting on day 2

Administer with food or on an empty stomach.
Administer at approximately the same time each day.
*dose adjustment may be required for some drug interactions

Following a dose interruption more than 7 days: when treatment resumes, repeat loading dose of 360 mg, followed by 120 mg once daily thereafter.

Concurrent radiation: has been used[2,14]

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BC Cancer usual dose noted in ***bold, italics***

Dosage in renal failure:	CrCl ≥15 mL/min: no dose adjustment required[2] CrCl <15 mL/min: no information found calculated creatinine clearance = N* x (140 - Age) x weight in kg / serum creatinine in micromol/L * For males N=1.23; for females N=1.04
Dosage in hepatic failure:	mild to moderate impairment (Child-Pugh A or B): no dose adjustment required[2] severe impairment (Child-Pugh C): no information found
Dosage in dialysis:	no information found

Children: safety and efficacy have not been established

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