PDL DRUG REVIEW

Proprietary Name: Orgovyx®
Common Name: relugolix
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Eligard	Recommended with Conditions
Lupron Depot	Recommended with Conditions

Summary

Pharmacology/Usage: Relugolix, the active ingredient of Orgovyx®, is a nonpeptide small molecule gonadotropin-releasing hormone (GnRH) receptor antagonist that competitively binds to pituitary GnRH receptors. Thus, it reduces the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently testosterone.

Indication: For the treatment of adult patients with advanced prostate cancer.

There is no pregnancy category for this medication; however, the risk summary indicates that the safety and efficacy of Orgovyx® have not been established in females. Based on findings in animals and mechanism of action, Orgovyx® can cause fetal harm and loss of pregnancy when administered to a pregnant female. There are no human data on the use of Orgovyx® in pregnant females to inform the drug-associated risk. Advise patients of the potential risk to the fetus. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of Orgovyx®. The safety and efficacy of use in pediatric patients have not been established.

Dosage Form: Tablets: 120mg. Do not crush or chew tablets; swallow tablets whole.

Recommended Dosage: Start with a loading dose of 360mg on the first day and continue treatment with a 120mg dose taken QD at about the same time each day. Take with or without food. If treatment with Orgovyx® is interrupted for greater than 7 days, restart Orgovyx® with a loading dose of 360mg on the first day and continue with a dose of 120mg QD.

In patients treated with gonadotropin-releasing hormone (GnRH) receptor agonists and antagonists for prostate cancer, treatment is usually continued upon development of non-metastatic or metastatic castration-resistant prostate cancer.

Clinically meaningful differences in the pharmacokinetics of relugolix were not seen based on mild to severe renal impairment or mild to moderate hepatic impairment. The effect of end-stage renal disease with or without hemodialysis or severe hepatic impairment on the pharmacokinetics of relugolix has not been evaluated.

Drug Interactions: Co-administration of Orgovyx® with a P-gp inhibitor increases the AUC and the maximum concentration (Cmax) of relugolix, which may increase the risk of adverse reactions associated with Orgovyx®. Avoid

co-administration of Orgovyx® with oral P-gp inhibitors. If co-administration is unavoidable, take Orgovyx® first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions. Treatment with Orgovyx® may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors. If treatment with Orgovyx® is interrupted for more than 7 days, resume administration of Orgovyx® with a 360mg loading dose on the first day, followed by 120mg QD.

Co-administration of Orgovyx® with a combined P-gp and a strong CYP3A inducer decreases the AUC and Cmax of relugolix, which may reduce the effects of Orgovyx®. Avoid coadministration of Orgovyx® with combined P-gp and strong CYP3A inducers. If co-administration is unavoidable, increase the Orgovyx® dose to 240mg QD. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended dose of Orgovyx® once daily.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Orgovyx®) minus reported % incidence for leuprolide acetate for all grades. Please note that an incidence of 0% means the incidence was the same as or less than comparator.* The most frequently reported adverse events included hot flush (2%), musculoskeletal pain (1%), fatigue (2%), diarrhea (5%), and constipation (2%). Laboratory abnormalities included glucose increased (0%), triglycerides increased (0%), ALT increased (0%), AST increased (0%), and hemoglobin decreased (0%).

Androgen deprivation therapy, such as Orgovyx® may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, or frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

Therapy with Orgovyx® results in suppression of the pituitary gonadal system. Results of the diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after Orgovyx® may be affected. The therapeutic effect of Orgovyx® should be monitored by measuring serum concentrations of prostate specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Myovant Sciences, Inc

Analysis: The safety and efficacy of Orgovyx® were assessed in a randomized, open-label study (HERO study; N=934) that included men with advanced prostate cancer requiring at least 1 year of androgen deprivation therapy and defined as biochemical (PSA) or clinical relapse following local primary intervention, newly diagnosed castration-sensitive metastatic disease, or advanced localized disease.

Patients were randomized to receive Orgovyx® or leuprolide for 48 weeks. Serum testosterone concentrations were measured at screening; on days 1, 4, 8, 15, and 29 in the first month; then monthly until the end of the study. The population across both treatment groups had a median age of 71 years (range 47 to 97 years), while 68% were white. Disease stage was distributed as follows: 32% metastatic (M1), 31% locally advanced, 28% localized, and 10% not classifiable. The median testosterone concentration at baseline across the treatment groups was 408ng/dL.

The major efficacy outcome measure was medical castration rate defined as achieving and maintaining serum testosterone suppression to castrate levels (<50ng/dL) by day 29 through 48 weeks of treatment. Other endpoints included castration rates on day 4 and 15 and castration rates with testosterone <20ng/dL at day 15. Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Outcome	Orgovyx® (N=622)	Leuprolide (N=308)
Castration rate, from day 29 through week 48	96.7%	88.8%

The % of patients attaining testosterone decreases within the first 29 days can be seen in the table below, which was adapted from the prescribing information.

	Testosterone <50ng/dL		Testosterone <20ng/dL	
	Orgovyx® (N=622)	Leuprolide Acetate (N=308)	Orgovyx® (N=622)	Leuprolide Acetate (N=308)
Day 4	56%	0%	7%	0%
Day 8	91%	0%	27%	0%
Day 15	99%	12%	78%	1%
Day 29	99%	82%	95%	57%

In the clinical trial, PSA levels were monitored and were lowered on average by 65% two weeks after administration of Orgovyx®, 83% after 4 weeks, 92% after 3 months, and remained suppressed throughout the 48 weeks of treatment. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. No evidence has shown that the rapidity of PSA decline is related to a clinical benefit.

A sub-study was conducted in 137 patients who did not receive subsequent androgen deprivation therapy for at least 90 days after discontinuation of Orgovyx®. Based on Kaplan-Meier analyses, 55% of patients achieved testosterone levels above the lower limit of the normal range (>280ng/dL) or baseline at 90 days after discontinuation of Orgovyx®.

Place in Therapy: Orgovyx® is an oral nonpeptide small molecule GnRH receptor antagonist indicated for the treatment of adult patients with advanced prostate cancer. Androgen deprivation therapy, such as Orgovyx®, may prolong the QT/QTc interval. Electrolyte abnormalities should be corrected, and periodic monitoring of electrocardiograms and electrolytes should be considered. In a clinical study compared with leuprolide, Orgovyx® resulted in a significantly greater proportion of patients with sustained testosterone suppression to castration levels by day 29 through 48 weeks of treatment; this difference between treatments of 7.9% met the criteria for both non-inferiority and superiority of relugolix ($p<0.001$ for superiority).[2] However, the rapidity of PSA decline has not yet been shown to have clinical benefit compared with current treatment.

It is recommended that Orgovyx® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use, as well as trials of recommended agents.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Orgovyx [package insert]. Brisbane, CA: Myovant Sciences, Inc; 2020.
[2] Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *NEJM*. 2020; 382(23): 2187-2196.