NEW DRUG APPROVAL

Brand Name	Orgovyx™
Generic Name	relugolix
Drug Manufacturer	Myovant Sciences, Inc

New Drug Approval

FDA Approval Date: December 18, 2020

Review Designation: Priority

Type of Review: Type 1 - New Molecular Entity

Dispensing Restriction: Specialty Only, Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Prostate cancer is cancer that occurs in the prostate. The prostate is a small walnut-shaped gland in males that produces the seminal fluid that nourishes and transports sperm. Many prostate cancers grow slowly and are confined to the prostate gland, where they may not cause serious harm. However, while some types of prostate cancer grow slowly and may need minimal or even no treatment, other types are aggressive and can spread quickly.

Advanced prostate cancer is cancer that has spread from the prostate to other parts of the body. It develops when prostate cancer cells move through the blood stream or lymphatic system.

Prostate cancer is often grouped into four stages.

- Stages I & II: The tumor has not spread beyond the prostate. This is often called “early stage” or “localized” prostate cancer.
- Stage III: Cancer has spread outside the prostate, but only to nearby tissues. This is often called “locally advanced prostate cancer.”
- Stage IV: Cancer has spread outside the prostate to other parts such as the lymph nodes, bones, liver or lungs. This stage is often called “advanced prostate cancer.”

It is the most common type of cancer in men, other than skin cancer. Approximately 1 in 9 men will be diagnosed with prostate cancer in their lifetime, and about 1 in 41 men will die of this disease. It is more likely to develop in older men (65 years of age and older) and in African-American men. The average age at diagnosis is about 66.

Efficacy

HERO: A Multinational Phase 3 Randomized, Open-label, Parallel Group Study to Evaluate the Safety and Efficacy of Relugolix in Men With Advanced Prostate Cancer (NCT03085095): [8]

The safety and efficacy of Orgovyx™ was evaluated in HERO (NCT03085095), a randomized, open label study in 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. A total of 934 patients were randomized to receive Orgovyx™ or leuprolide 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) Leuprolide acetate 22.5 mg injection (or 11.25 mg in Japan and Taiwan) subcutaneously every 3 months. Leuprolide acetate 11.25 mg is a dosage regimen that is not recommended for this indication in the US.

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 (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 median testosterone concentration at baseline across the treatment groups was 408 ng/dL.

The major 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. Other endpoints included castration rates on Day 4 and 15 and castration rates with testosterone < 20 ng/dL at Day 15.

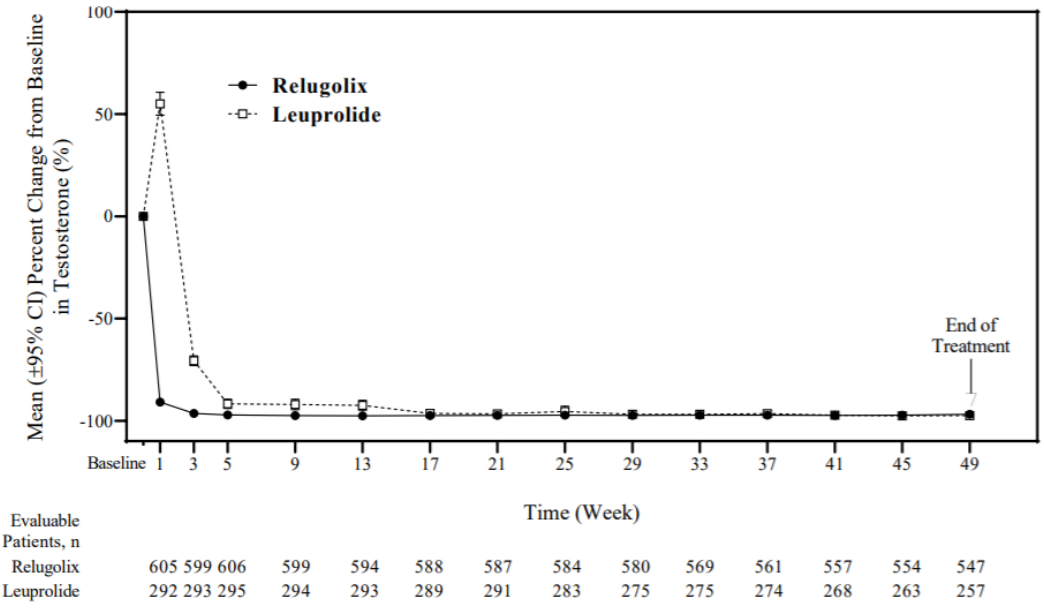
The efficacy results are shown in Table 3 and the time course of percent change from baseline in testosterone suppression by Orgovyx™ and leuprolide during the 48 week treatment period are shown in Figure 2.

Table 3: Medical Castration Rates (Testosterone Concentrations < 50 ng/dL) from Day 29 through Week 48 in HERO

	ORGOVYX 360/120 mg (N = 622)[b]	Leuprolide Acetate 22.5 or 11.25 mg[a] (N = 308)[b]
Castration Rate (95% CI)[c]	96.7% (94.9%, 97.9%)	88.8% (84.6%, 91.8%)

[a] 11.25 mg is a dosage regimen that is not recommended for this indication in the US. The castration rate of the subgroup of patients receiving 22.5 mg leuprolide (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.

Figure 2: Mean (95% CI) Percent Change from Baseline in Testosterone Concentrations from Baseline to Week 49 by Treatment Group in HERO



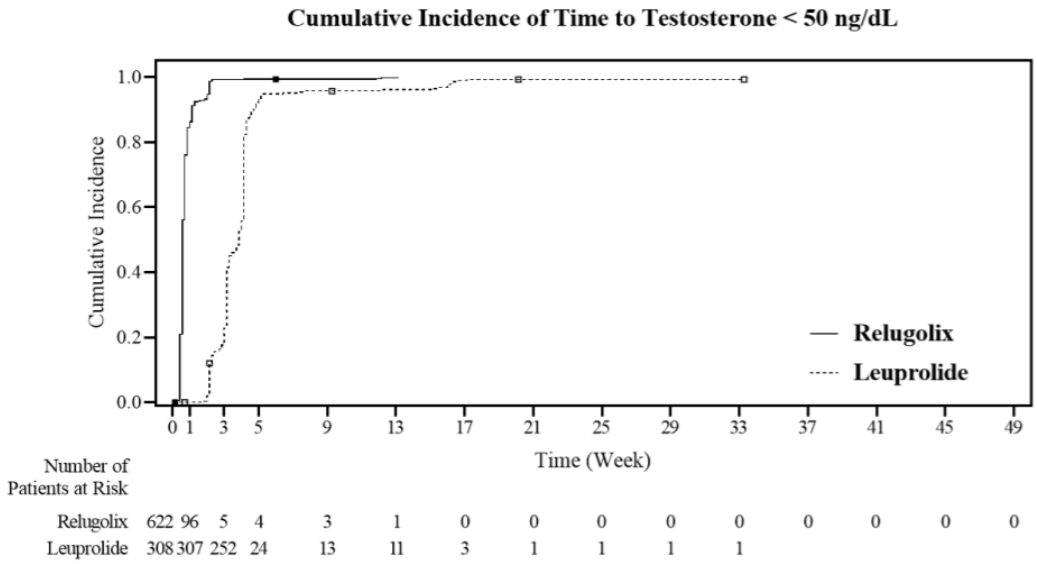
The percentages of patients who attained the medical castration levels of testosterone < 50 ng/dL and < 20 ng/dL within the first 29 days of treatment are summarized in Table 4 and the cumulative incidences of time to testosterone < 50 ng/dL or < 20 ng/dL are shown in Figure 3.

Table 4: Percentage of Patients Attaining Testosterone Decreases within the First 29 Days in HERO[a]

	Testosterone < 50 ng/dL		Testosterone < 20 ng/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%

[a] Kaplan-Meier estimates within group.

Figure 3: Cumulative Incidence of Time to Testosterone < 50 ng/dL and < 20 ng/dL in HERO



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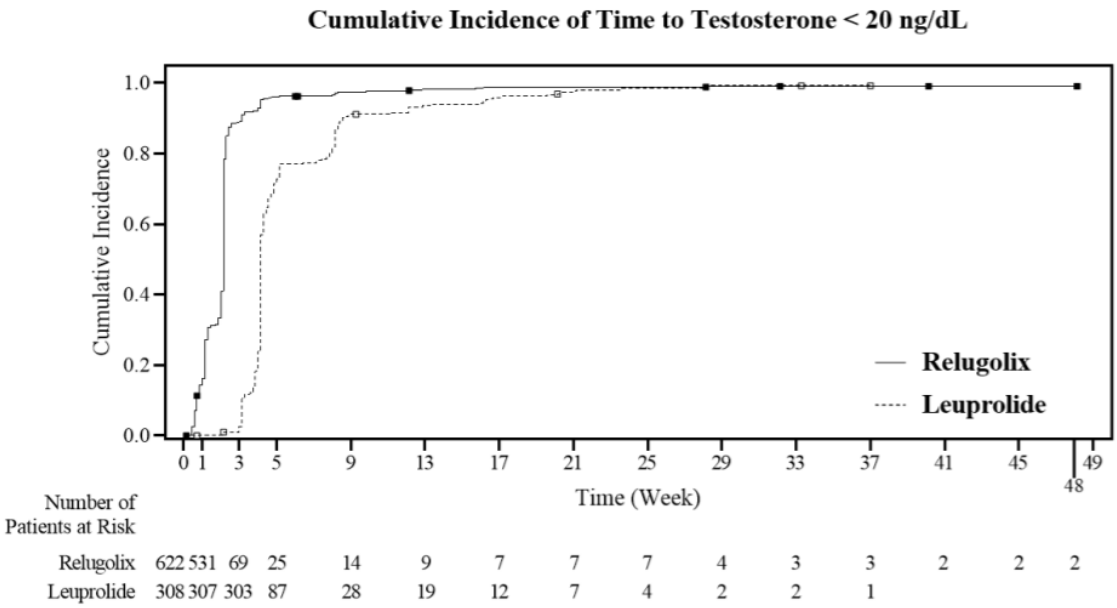

In the clinical trial, PSA levels were monitored and were lowered on average by 65% two weeks after administration of Orgovyx™, 83% after 4 weeks, 92% after 3 months and remained suppressed throughout the 48 weeks of treatment. These PSA results should be interpreted with caution because of the heterogeneity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

A substudy 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 (> 280 ng/dL) or baseline at 90 days after discontinuation of Orgovyx™.

Safety

ADVERSE EVENTS

The most common adverse reactions (≥ 10%) and laboratory abnormalities (≥ 15%) were hot flush, glucose increased, triglycerides increased, musculoskeletal pain, hemoglobin decreased, alanine aminotransferase (ALT) increased, fatigue, aspartate aminotransferase (AST) increased, constipation, and diarrhea.

WARNINGS & PRECAUTIONS

QT/QTc Interval Prolongation: 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.

Embryo-Fetal Toxicity: 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. In an animal reproduction study, oral administration of relugolix to pregnant rabbits during the period of organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on area under the curve (AUC).

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of Orgovyx™.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to pituitary GnRH receptors, thereby, reducing the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and consequently testosterone.

Dose & Administration

ADULTS

360 mg loading dose orally on day 1, followed by 120 mg once daily at approximately the same time each day; usually continued upon development of nonmetastatic or metastatic castration-resistant prostate cancer.

If therapy interruption of greater than 7 days, restart with a loading dose of 360 mg on day 1 and continue with of 120 mg once daily.

PEDIATRICS

The safety and efficacy of Orgovyx™ in pediatric patients have not been established.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

None.

HEPATIC IMPAIRMENT

None.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 120 mg