

Company

Myovant Sciences, Inc.

Drug or Device Name

ORGOVYX™ (relugolix)

Category

Pharmaceutical

Compound/Technical Name

TAK-385

Trade Name

ORGOVYX™

Date of Approval

12/18/2020

Therapeutic Categories

N/A

Indications

On December 18, 2020, the Food and Drug Administration approved the first oral, once-daily gonadotropin-releasing hormone receptor antagonist, ORGOVYX™ (relugolix) for adult patients with advanced prostate cancer. With over 248,000 estimated new prostate cancer diagnoses in men in the United States (US) in 2021, prostate cancer accounts for more than 1 in 4 of new cancer diagnoses and represents the most commonly diagnosed cancer in men. Prostate cancer incidence increases with age and the median age at diagnosis of prostate cancer is 67 years in the US. Prostate cancer incidence and mortality rates are increased in men of African descent; these observations have previously been attributed to a wide range of factors, including genes and environment. As a result of the US prostate cancer screening program, the majority (76%) of prostate cancers are localized at diagnosis and have a good prognosis, with an estimated 5-year survival rate of >99%. However, patients with metastatic disease have an estimated 5-year survival rate of 30%. Commensurate with the introduction of screening in 1992, prostate cancer mortality fell steeply (52%) between 1993-2018, but has since increased, possibly due to an increase in the proportion of patients diagnosed with metastatic disease, which, in turn, may have resulted from a US government-recommended reduction in prostate cancer screening between 2012-2018. At 34,130, the projected prostate cancer mortality rate in 2021 represents the highest level in 20 years and prostate cancer remains the second most common cause of cancer death in men in the US. Treatment options for patients include active surveillance, surgery, radiation and/or hormonal therapy to reduce levels of the male hormones that can stimulate tumor growth (androgen-deprivation therapy). For advanced or metastatic prostate cancer, chemotherapy is also a treatment option.

Background

Androgen-deprivation therapy (ADT) is the foundation of medical therapy for advanced prostate cancer. In 2021, approximately 300K and 100K men in the US are expected to be treated with or initiate ADT, respectively. Luteinizing hormone-releasing hormone (LHRH) agonists are the most widely used ADT. Gonadotropin-releasing hormone (GnRH) binds to the receptors of the pituitary gland and stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. Release of LH subsequently stimulates the testes to produce testosterone. Initial administration of a LHRH agonist increases LH and FSH and, thereby, testosterone. Long-term or chronic exposure to a LHRH agonist desensitizes the receptors, leading to LH and testosterone suppression, with partial FSH suppression. The acute testosterone surge associated with LHRH agonists may lead to an exacerbation of clinical symptoms in men with advanced disease, including increased bone pain, spinal cord compression, bladder output obstruction and even death. GnRH receptor antagonists like Orgovyx block GnRH receptors, achieving immediate LH and FSH suppression and avoiding testosterone surge. Until 2020, only depot injectable ADT formulations were available. In addition to potential injection site reactions, most ADTs are associated with long testosterone recovery times after discontinuation of treatment. Androgen deprivation is associated with hot flashes, fatigue, sexual dysfunction, pain, osteoporosis, and metabolic alterations. To reduce these effects, intermittent ADT, has been investigated and showed improved quality of life, sexual outcomes, and morbidity, without meaningful effects on oncological outcomes and with reduced healthcare costs. Metabolic changes associated with ADT are associated over time with increased risk for cardiovascular (CV) events. Some studies showed that LHRH agonists are associated with an additional early increased risk of CV events. Since 2010, the FDA-approved labels of LHRH agonists carry a warning about increased risk of certain CV diseases and diabetes. Myovant Sciences is a wholly owned subsidiary of Sumitovant Biopharma Ltd.

Development

Identifying an oral GnRH receptor antagonist for development was always challenging, as the first generation of GnRH receptor antagonists inevitably have peptide structures that undergo enzymatic degradation by intestinal enzymes and therefore cannot be administered orally. Because relugolix is a small molecule i.e., a non-peptide, it can be absorbed after oral administration. Relugolix, first known as TAK-385, has good GnRH binding specificity, and potent in vitro and in vivo GnRH antagonistic activity, without CYP inhibition. In preclinical studies, daily oral administration of relugolix was shown to potently, continuously, and reversibly suppress the hypothalamic-pituitary-gonadal axis and was selected for development and demonstrated dose-proportional exposure with oral administration, with rapid, sustained, and reversible testosterone suppression to castrate levels (<50 ng/dL). In phase 2 evaluation relugolix achieved rapid and sustained testosterone suppression. Relugolix achieved castrate testosterone levels as effectively, but more rapidly, than the GnRH agonist leuprolide, while avoiding the initial testosterone surge. In another study, relugolix demonstrated similar levels of testosterone suppression as degarelix and the safety profile was consistent with testosterone suppression. These results supported the further clinical development and assessment of relugolix in phase III testing. The phase 3 HERO trial of relugolix, which included 930 men with advanced prostate cancer, represents one of the largest ADT studies ever reported. In this study, relugolix achieved a rapid and sustained testosterone suppression, sustained testosterone suppression to profound castrate levels (<20 ng/dL), and included a prespecified exploratory safety analysis of major adverse cardiovascular events. These trial data, published in the New England Journal of Medicine (Shore N, 2020 NEJM 382:23), supported the recent FDA approval of Orgovyx for the treatment of patients with advanced prostate cancer.

Innovation

CV events are the leading cause of death in men with prostate cancer. Approximately 25% of men with prostate cancer have CV disease, with many more having risk factors, such as hypertension. Some studies show LHRH agonists can increase the CV burden; in a meta-analysis of data from 491,258 men, the use of LHRH agonists was shown to increase relative risk of non-fatal myocardial infarction by 57% and stroke by 51% (Bosco, 2015 Eur Urol 68;3). As well as avoiding acute hormone surge, GnRH antagonists have the potential to offer a reduced CV burden compared with LHRH agonists; in a meta-analysis of data from 2,328 men, the risk of cardiac events within 1-year of initiating GnRH antagonist therapy was less than half that with LHRH agonists (Albertsen PC, 2014 Eur Urol 65;3). Orgovyx represents the only oral GnRH antagonist developed for treatment of advanced prostate cancer (previously elusive due to the low aqueous solubility of peptide GnRH antagonists). With the approval of Orgovyx, men with advanced prostate cancer now have a once-a-day treatment option with demonstrated efficacy and safety, including a 96.7% response rate in testosterone suppression through 48 weeks. In addition, the phase 3 HERO study included an exploratory safety analysis assessing cumulative incidence of major adverse cardiovascular events compared to leuprolide injections, the current standard of care. These results have the potential to greatly inform physicians and patients when they are weighing the benefits and risks of ADT options. The practice-changing potential of Orgovyx is further supported by inclusion of the HERO trial in the New England Journal's selection of the most notable articles in 2020. From its launch in January 2021 to April 2021, demand for Orgovyx among urologists and oncologists ramped up quickly with >800 treatment centers prescribing the therapy to >2,000 patients.

Pubmed

1. Dearnaley DP, Saltzstein DR, Sylvester JE, et al. The Oral Gonadotropin-releasing Hormone Receptor Antagonist Relugolix as Neoadjuvant/Adjuvant Androgen Deprivation Therapy to External Beam Radiotherapy in Patients with Localised Intermediate-risk Prostate Cancer: A Randomised, Open-label, Parallel-group Phase 2 Trial. *Eur Urol*. Aug 2020;78(2):184–192. <https://pubmed.ncbi.nlm.nih.gov/32273183>. 2. MacLean DB, Shi H, Faessel HM, Saad F. Medical Castration Using the Investigational Oral GnRH Antagonist TAK-385 (Relugolix): Phase 1 Study in Healthy Males. *J Clin Endocrinol Metab*. Dec 2015;100(12):4579–4587. <https://pubmed.ncbi.nlm.nih.gov/26502357>. 3. Shore ND, Saad F, Cookson MS, et al. Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer and Supplementary Material. *N Engl J Med*. Jun 2020;382(23):2187–2196. <https://www.ncbi.nlm.nih.gov/pubmed/32469183>. 4. Suzuki H, Uemura H, Mizokami A, et al. Phase I trial of TAK-385 in hormone treatment-naïve Japanese patients with nonmetastatic prostate cancer. *Cancer Med*. Oct 2019;8(13):5891–5902. <https://pubmed.ncbi.nlm.nih.gov/31429205>.

Attachments

- 1624917139Orgovyx_package_insert.pdf
- 1624917148FDA_approval_letter.pdf
- 1624917216LHRH_agonist_vs_GnRH_antagonist.pdf
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