relugolix (Orgovyx™)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO228

Description
Relugolix is an orally administered gonadotropin-releasing hormone (GnRH) antagonist.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
relugolix (Orgovyx)	120 mg tablets	Prostate cancer	**Initial**: 30 tablets/28 days for one month **Maintenance**: 30 tablets/30 days

Initial Evaluation

I. **Relugolix (Orgovyx)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
   C. A diagnosis of **prostate cancer**; **AND**
      1. Provider attestation the member is castration sensitive; **AND**
      2. Prostate cancer is advanced or metastatic (Stage III or IV); **AND**
      3. Treatment with a GnRH agonist (e.g., leuprolide [Lupron]), has been ineffective, not tolerated, or all GnRH agonists are contraindicated; **OR**
         i. The member has a history of a major adverse cardiovascular event (MACE) (e.g., myocardial infarction, stroke); **AND**
      4. Degarelix (Firmagon) has been ineffective, not tolerated, or is contraindicated; **AND**
   D. Relugolix (Orgovyx) is medically necessary for the treatment of prostate cancer over GnRH agonists and degarelix (Firmagon) [documentation of medically necessity is verified by a clinical pharmacist at the health plan]. (Note – preference for oral administration or other convenience does not meet medical necessity)

II. Relugolix is considered investigational when used for all other conditions, including but not limited to:
    A. Castration-resistant prostate cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If so, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
    A. Documentation of disease response to treatment (e.g., stabilization of disease or decrease in tumor size or tumor spread, reduction in serum testosterone or PSA); **OR**
    B. Provider attestation that continuation of therapy is necessary if the member has had disease progression

Supporting Evidence

I. Relugolix (Orgovyx) is a gonadotropin-releasing hormone (GnRH) receptor antagonist, FDA-approved for the treatment advanced prostate cancer. A 360 mg loading dose (three tablets) is administered on day one, then a maintenance dose of 120 mg (one tablet) is taken once daily. It is one of several androgen deprivation therapies (ADT) available. Other options include GnRH agonists such as leuprolide (Lupron), goserelin (Zoladex), triptorelin (Telstar/Triptodur), histrelin (Supprelin LA, Vantas), and GnRH agonist [degarelix (Firmagon)], all of which are injectable medications. Additionally, surgical orchiectomy is an option when prompt castration is required. Reducing serum testosterone to castrate levels is warranted for the treatment of prostate cancer, and all of these methods are highly effective. Androgen deprivation therapy is a hallmark of treatment, and is generally continued, if tolerated, even if there is progressive disease and/or if other prostate cancer medications are started. Given the specialization of the condition and treatment options, therapy should be prescribed by, or in consultation with, an oncologist.
II. The GnRH agonists are highly utilized for the treatment of advanced or metastatic prostate cancer. They are known to cause a testosterone surge upon initiation, with a subsequent decrease in serum testosterone three-to-four weeks after starting treatment. For patients at risk for these symptoms, an antiandrogen therapy (e.g., flutamide, nilutamide, bicalutamide) may be administered concurrently for the first few weeks of GnRH agonist treatment. Some agents are available in every-three-month injections and are generally well tolerated

III. The GnRH antagonists, degarelix (Firmagon), and now relugolix (Orgovyx), are successful at mitigating the testosterone surge and may rapidly reduce testosterone; although, the rapidity of testosterone suppression with GnRH antagonists has not been linked to superior clinical benefit over the GnRH agonists in the general population likely to utilize these therapies.

IV. Relugolix (Orgovyx) was evaluated in one Phase 3, randomized, open-label, non-inferiority (NI) trial vs. leuprolide (Lupron) over 48 weeks in patients with advanced or metastatic disease. Up to 13% of patients had previous ADT, 30% had previous radiotherapy, and 14% had a history of major adverse cardiovascular event (MACE). There was a washout period of three months for those previously treated with degarelix (Firmagon) and one year for those on GnRH agonist therapy. Those with a MACE in the six months before the trial were excluded. All patients included in the trial were adults, which is the expected population to be diagnosed with prostate cancer. At this time the safety and efficacy of relugolix (Orgovyx) in pediatric patients remains unknown; however, it would be very rare for a pediatric patient to develop prostate cancer.

V. The primary outcome was cumulative sustained castration rate of less than 50 ng/dL from day 29 through 48 weeks. Results were 96.7% of patients for relugolix (Orgovyx) and 88.8% for leuprolide (Lupron), with a difference of 7.9% (CI 4.1-11.8). Additionally, a notable secondary outcome was castration relapse free survival (CRFS) at 48 weeks. This was 74% for relugolix (Orgovyx) and 75% for leuprolide (Lupron) (HR 1.03, CI 0.68-1.57, p=0.84). Both of these outcomes showed NI of relugolix (Orgovyx) to leuprolide (Lupron). Statistically, relugolix (Orgovyx) was superior to leuprolide (Lupron) in the primary outcome; however, both therapies showed a very high rate of sustained castration. At this time definitive data are lacking to indicate clinical superiority of either product in regard to medication efficacy.

VI. There were several other secondary outcomes measured: probability of testosterone suppression to less than 50 ng/dL on day four and day 15, prostate specific antigen (PSA) response on day 15 and day 29, probability of profound testosterone suppression (less than 20 ng/dL) on day 15. These were all superior for relugolix (Orgovyx) over leuprolide (Lupron). This is expected given the mechanistic differences of the therapies. Given the known initial testosterone surge with GnRH agonists, castrate levels would be expected three-to-four weeks after medication initiation. The results confirm the rapidity of testosterone suppression for relugolix (Orgovyx), as expected for a GnRH antagonist.

VII. Rate of overall adverse events (AE) was consistent across both groups. Common AE (greater than 10%) that occurred in both groups included laboratory abnormalities, increase glucose levels, increase triglycerides, musculoskeletal pain, increased hemoglobin, ALT/AST increases, constipation, and diarrhea.

VIII. Serious AE occurred in 9.8% of the relugolix (Orgovyx) group, and 15.3% of the leuprolide (Lupron) group. For relugolix (Orgovyx) sAE: myocardial infarction (0.8%), AKI (0.6%), hemorrhage (0.6%), and UTI (0.5%).

IX. The MACE rate was 2.9% for relugolix (Orgovyx) and 6.2% for leuprolide (Lupron), overall. This was further pronounced in the subgroup of patients that had a previous MACE. Rates were 3.6%

and 17.8%, respectively. In the group without a previous MACE, rates were 2.8% and 4.2%, respectively. From the data, it is predicted that GnRH antagonists may have a favorable safety profile in those with history of a MACE, such as myocardial infarction and stroke. Options include degarelix (Firmagon) as well as relugolix (Orgovyx), and current data are lacking to indicate clinical favorability between these two agents.

Investigational or Not Medically Necessary Uses

I. Relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Castration-resistant prostate cancer

References

1. Shore N., Saad F., Cookson M., et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. *N Engl J Med.* 2020;382(23):2187-2196.
2. Orgovyx [Prescribing Information]. Myovant Sciences, Inc. Brisbane, CA. December 2020.
3. National Comprehensive Cancer Network, NCCN Guidelines. Prostate Cancer. V.3.2020. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Updated November 17, 2020.
4. PDQ Adult Treatment Editorial Board. PDQ Prostate Cancer Treatment. Bethesda, MD: National Cancer Institute. Updated December 10, 2020. Available at: https://www.cancer.gov/types/prostate/hp/prostate-treatment-pdq. Accessed January 25, 2021 [PMID: 26389471]
5. Lowrance WT, Breau RH, Chou R et al: Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART I and II. J Urol 2021; 205: 14, 22.
6. Firmagon [Prescribing Information]. Ferring Pharmaceuticals. Parisppany, NJ. February 2015.
7. Lupron Depot [Prescribing Information]. Abbvie Inc. Chicago, IL. January 2019.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
GnRH Antagonists in Gynecologic Conditions	Heavy menstrual bleeding associated with uterine fibroids (leiomyoma) Moderate to severe pain associated with endometriosis
Gonadotropin-releasing hormone (GnRH)	Endometriosis, Central Precocious Puberty (CPP), Advanced Prostate Cancer, Uterine leiomyoma (fibroids), Advanced breast cancer in premenopausal women, Reduction of endometrial thickness prior to endometrial ablation, Gender Dysphoria

Policy Implementation/Update:

Action and Summary of Changes	Date
Myfembree moved to GnRH Antagonists in Gynecologic Conditions policy for uterine fibroids and moderate to severe pain with endometriosis; Endometriosis removed from E/I section; Changed policy name to relugolix (Orgovyx)	11/2022
Policy created	05/2021