Relugolix (Orgovyx®) for the treatment of advanced hormone-sensitive prostate cancer

General information [1]

Drug description	Indication
Relugolix (Orgovyx®) is a hormone antagonist that competitively binds to gonadotropin-releasing hormone (GnRH) receptors in the anterior pituitary gland, preventing native GnRH from binding. This reduces the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), causing a reduction in the production of testosterone from the testes.	Relugolix (Orgovyx®) is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer.

Current treatment [2]

- ESMO treatment recommendations for metastatic hormone-naive prostate cancer:
  - Androgen deprivation therapy (ADT) is recommended as first-line treatment of metastatic hormone-naive prostate cancer in combination with abiraterone/prednisone (ESMO-MCBS v1.1 score: 4) or apalutamide (ESMO-MCBS v1.1 score: 4) or docetaxel (ESMO-MCBS v1.1 score: 4) or enzalutamide (ESMO-MCBS v1.1 score: 4).
  - Radiotherapy to the primary tumour combined with the systemic treatment is recommended for patients with low-volume metastatic hormone-naive prostate cancer.
  - ADT alone is recommended as first-line systemic treatment of metastatic hormone-naive prostate cancer in men who are unfit for abiraterone, apalutamide, enzalutamide and docetaxel.
  - For men starting on ADT, management to prevent cancer treatment-induced bone loss is recommended.

Regulatory status

EMA	FDA [3, 4]
Approval status for this indication: On 24 February 2022, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Orgovyx®. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 29/04/2022 The full indication is: ❖ Orgovyx® is indicated for the treatment of adult patients with advanced hormone-sensitive prostate cancer. **Other indications**: none ✓ **Medicine is under additional monitoring**	**Approval status for this indication**: On 18 December 2020, the FDA approved the first oral GnRH receptor antagonist, relugolix (Orgovyx®) for adult patients with advanced prostate cancer. ✓ Priority review **Other indications**: MYFEMBREE®, indicated for the management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal women is a combination of relugolix, estradiol and norethindrone acetate.

Costs

30 Orgovyx® tablets 120 mg = € 210.00 (ex-factory price) [5]

Warnings and precautions [6, 7]

- **QT/QTc interval prolongation**
  - Androgen deprivation therapy may prolong the QT interval.
- **Embryo-foetal toxicity**
  - Orgovyx® can cause foetal harm. Advise males with female partners of reproductive potential to use effective contraception.
- **Cardiovascular disease**

- Cardiovascular disease such as myocardial infarction and stroke has been reported in the medical literature in patients with androgen deprivation therapy. Therefore, all cardiovascular risk factors should be taken into account.

❖ **Changes in bone density**

- Long-term suppression of testosterone in men who have had orchiectomy or who have been treated with a GnRH receptor agonist or GnRH antagonist is associated with decreased bone density.
- Decreased bone density, in patients with additional risk factors, may lead to osteoporosis and increased risk of bone fracture.

❖ **Hepatic impairment**

- Patients with known or suspected hepatic disorder have not been included in long-term clinical trials with relugolix. Mild, transient increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been observed but were not accompanied by an increase in bilirubin or associated with clinical symptoms.
- Monitoring of liver function in patients with known or suspected hepatic disorder is advised during treatment.
- The pharmacokinetics of relugolix in patients with severe hepatic impairment has not been evaluated.

❖ **Severe renal impairment**

- The exposure to relugolix in patients with severe renal impairment may be increased by up to 2-fold.
- Because a lower dose of relugolix is not available, caution in patients with severe renal impairment is warranted upon administration of a 120-mg dose of relugolix once daily.
- The amount of relugolix removed by haemodialysis is unknown.

❖ **Prostate-specific antigen (PSA) monitoring**

- The effect of Orgovyx® should be monitored by clinical parameters and prostate-specific antigen (PSA) serum levels.

❖ **Sodium**

- This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Study characteristics [8-10]

Trial name	*n*	Intervention (I), n=622	Comparator (C), n=308	PE	Characteristics	Biomarker	Funding	Publication(s)
HERO NCT03085095	934 2:1	relugolix 120 mg orally once daily for 48 weeks (after a single oral loading dose of 360 mg)	leuprolide injections every 3 months for 48 weeks	sustained castration rate[1]	multinational, randomised, open-label[2], phase 3 trial	-	Myovant Sciences	[10]

Efficacy (I vs. C)

The **median follow-up time** in both groups, including the 30-day safety follow-up period for AEs was **52 weeks**.
Sustained testosterone suppression below castrate levels (<50 ng per deciliter) from day 29 through 48 weeks was achieved in: 96.7% (95% CI, 94.9-97.9) vs. 88.8% (95% CI, 84.6-91.8)
Between-group difference: 7.9 percentage points; 95% CI, 4.1-11.8, p<0.001
Cumulative probability of castration on day 4: 56.0% vs. 0%, p<0.001
Cumulative probability of castration on day 15: 98.7% vs. 12.0%, p<0.001
Cumulative probability of profound testosterone suppression to <20 ng/dl on day 15: 78.4% vs. 1.0%, p<0.001
PSA response at day 15 followed by confirmation at day 29: 79.4% vs.19.8%, p<0.001

Safety (I vs. C)

Any AEs grade ≥3: n=112/622 (18.0%) vs. n=63/308 (20.5%)
SAEs grade ≥3: n=61/622 (9.8%) vs. n=35/308 (11.4%)
Fatal AEs: n=7/622 (1.1%) vs. n=9/308 (2.9%)
MACE: n=8/622 (1.3%) vs. n=4/308 (1.3%)

[1] Defined as the cumulative probability of testosterone suppression to less than 50 ng per deciliter during receipt of trial treatment from day 29 through 48 weeks. Testosterone values for the primary end-point analysis were measured at a blinded central laboratory.
[2] Results not (yet) available for all prespecified endpoints.

Mean FSH level at end of week 24:1.72 IU/l vs. 5.95 IU/l, p<0.001					
ESMO-MCBS version 1.1 [11]					
The ESMO-MCBS was not applicable due to the given primary endpoint.					
Risk of bias (RCT) [12]					
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	no, open label	unclear[3]	yes[4]	unclear
First published: 03/2022 **Last updated**: 10/2022					

Abbreviations: ADT=androgen deprivation therapy AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, FSH=follicle-stimulating hormone, GnRH=gonadotropin-releasing hormone, HR=hazard ratio, I=intervention, Int.=intention, LH=luteinizing hormone, MACE=major adverse cardiovascular event, MG=median gain, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PSA=prostate-specific antigen, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

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[3] Results not (yet) available for all prespecified endpoints.
[4] Industry-funded trial.

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