Report FIRMAGON® degarelix

Product & Mechanism of action

Substance: degarelix

Brand Name: Firmagon

Originator/licensee: Ferring Pharmaceuticals A/S

Classification: NI

ATC code: L02BX02

Orphan Status:
Eu: -
Us: -

Mechanism of action:
Degarelix is a selective GnRH antagonist that competitively and reversibly binds to the pituitary GnRH receptors, thereby rapidly reducing the release of the gonadotrophins, LH and FSH, and thereby reducing the secretion of testosterone by the testes [1].

Authorized indications Licensing status

Authorized Indication:
EMA: degarelix is a GnRH antagonist indicated 1) for the treatment of high-risk localized and locally advanced hormone-dependent prostate cancer **in combination with radiotherapy** 2) as neo-adjuvant treatment **prior to radiotherapy** in pts with high-risk localized or locally advanced hormone-dependent prostate cancer [2].

Route of administration: IV

Licensing status
EMA MA date: 19/10/2021
FDA M.A. date: -

EU Speed Approval Pathway: -

ABBREVIATIONS:
ADT: androgen deprivation therapy
AEs: Adverse Events
BL: Baseline
CI: confidence interval
CHMP: Committee for Medicinal Products for Human Use
FSH: follicle stimulating hormone
GnRH: gonadotrophin releasing hormone
IV: Intravenous
LH: luteinizing hormone
M.A.: Marketing Authorization **P.O.:** Positive Opinion
PSA: prostate-specific antigen
Pts: patients
RT: radiotherapy
SAEs: Serious Adverse Events
SC: subcutaneous
SoC: Standard of Care
TEAEs: Treatment-Emergent Adverse Events
TPV: total prostate volume
vs.: versus

Essential therapeutic features

Summary of clinical EFFICACY:

Trial	Treatment arms	Primary endpoint	Results
Study 00006 (NCT01744366) open-label, multicenter, randomized, non-inferiority trial, in adult men with a histologically confirmed adenocarcinoma of the prostate, PSA level ≥2.0 ng/mL at screening and life expectancy of >1 year	-degarelix (n=142; starting dose of 240 mg administered at day 0 followed by 12 monthly -28-day intervals- maintenance doses of 80 mg), -goserelin (n=141; administered as 12 monthly doses)	Difference in 1-year cumulative probability of suppressing testosterone to ≤0.5 ng/mL. Non-inferiority was to be established if the lower 95% CI limit ≥ -10	The difference between the treatment arms was 3.6% (95% CI: −1.5%, 8.7%), demonstrating non-inferiority of degarelix. Probabilities of maintaining castrate testosterone levels was 97.0% (95% CI: 92.3%, 98.9%) in degarelix arm vs. 93.4% (95% CI: 87.7%, 96.5%) in goserelin arm [3].
Study CS30 (NCT00833248), randomized, parallel-arm, active controlled, open-label trial, in adult men with TPV>30 ml; scheduled to undergo radical RT treatment and in whom neoadjuvant ADT was indicated	-degarelix (n=181; 240 mg administered at day 0 and 80 mg at day 28, 56) -bicalutamide (n=65; 50 mg) was initiated on day 0 and continued for 17 days. Goserelin (n=65; 3.6 mg) administered at day 3, 31, 59.	The mean percentage reduction in TPV at 12 weeks as compared to BL.	TPV decreased from BL to week 12 of -36.0 ± 14.5% in degarelix arm vs. -35.3 ± 16.7% in the goserelin arm. The adjusted difference between treatment groups was -0.3% (95% CI -7.74; 4.14%) [3].

Summary of clinical SAFETY:
Study 00006: The incidence of TEAEs was higher with degarelix than with goserelin (76% vs. 59%, respectively). Predominantly general disorders and administration site conditions were reported in 52% of the degarelix pts vs. 8% of the goserelin pts. Pts with metastatic disease reported higher incidence of severe AEs in the goserelin group as compared to the degarelix group (14% vs. 7%, respectively). SAEs were reported by 12 pts (9%) treated with degarelix vs. 18 (13%) pts treated with goserelin. The most common SAEs were cardiac disorders, which occurred in five pts (4%) in the degarelix group vs. two pts (1%) in the goserelin group. Two pts (each one in each group) up had SAEs considered as treatment-related (acute kidney injury and lung infection possibly related to degarelix and femur fracture and haematuria possibly related to goserelin). Two pts (1%) receiving degarelix had increased PSA levels that were reported as SAEs, of which one SAE led to withdrawal of the patient from the study [3].
Study CS30: TEAEs were reported by 87 and 83% of pts in the degarelix and goserelin groups, respectively. TEAEs that were considered possibly/probably related to the drug were reported by 78 and 73% of pts, respectively. Most of the TEAEs were hot flushes (60% degarelix, 63% goserelin). Other commonly reported reactions were injection site reactions (pain [33%], erythema [25%], pruritus [7%] and swelling [6%]), which were reported in the degarelix group only, erectile dysfunction (8% degarelix, 9% goserelin), asthenia (7 and 9%), fatigue (6 and 9%) and decreased libido (7 and 6%). Serious AEs considered as probably/possibly related to the treatment were reported in two pts in the degarelix arm (liver enzyme elevations and urinary retention) [3].

Ongoing studies:
- ***For the same indication:*** Yes.
- ***For other indications:*** Yes.

Discontinued studies (for the same indication): No.

References:
1. https://www.ema.europa.eu/en/documents/product-information/firmagon-epar-product-information_en.pdf
2. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/firmagon
3. https://www.ema.europa.eu/en/documents/variation-report/firmagon-h-c-000986-ii-0039-g-epar-assessment-report-variation_en.pdf
4. https://gallery.farmadati.it/
5. https://www.aiom.it/wp-content/uploads/2020/12/2020_LG_AIOM_Carcinoma_Prostata.pdf
6. https://www.annalsofoncology.org/article/S0923-7534(20)39898-7/fulltext

NHS impact

Cost of therapy:
The Italian price for one injection of degarelix (80 mg vial for injectable solution) is 212.90 € [4].

Epidemiology:
In Italy, prostatic carcinoma is currently the most frequent neoplasm among men, and represents more than 20% of all tumors diagnosed around the 50th year of age. The largest proportion of pts has to be found in the North of the country (1,428 cases per 100,000 inhabitants in the Northwest and 1,395 in the Northeast, respectively) compared to the Center (1,015) and the South (588) [5].

POSSIBLE PLACE IN THERAPY
The SoC for high-risk localized and locally advanced hormone-dependant prostate cancer is neo-adjuvant ADT for 4-6 months (± neoadjuvant docetaxel), followed by electron beam radiotherapy + ADT and adjuvant ADT for the subsequent two years.
The alternative option includes radical prostectomy + pelvic lymphadenectomy [6].

OTHER INDICATIONS IN DEVELOPMENT: Yes (Endometriosis, Female infertility).

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: No.

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION: Yes (flutamide, apalutamide).
*Service reorganization Y/N: No
*Possible off label use Y/N: Yes

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