Degarelix (Firmagon®) as a neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone-dependent prostate cancer

General information

Drug description [1]	Indication [2]
Degarelix (Firmagon®) is a selective gonadotrophin releasing-hormone (GnRH) antagonist that competitively and reversibly binds to the pituitary GnRH receptors, thereby rapidly reducing the release of the gonadotrophins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and thereby reducing the secretion of testosterone by the testes.	Degarelix (Firmagon®) is indicated as a neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone-dependent prostate cancer.

Current treatment [3]

Management of local/locoregional disease

- There is no consensus regarding optimum management of the localised disease.
- Patients should be informed of the benefits and harms of the different options. Given the range of treatment options and their side effects, men should be offered the opportunity to consult with both a urologist and a radiation oncologist. Men should be counselled that treatment of prostate cancer may cause sexual dysfunction, infertility, bowel and urinary problems.
- Recommendations:
  - Watchful waiting with delayed androgen deprivation therapy (ADT) for symptomatic progression is an option for men who are not suitable for, or unwilling to have, radical treatment (I, A).
  - Active surveillance is recommended for men with low-risk disease (I, A).
  - Radical prostatectomy (RP) or radiotherapy (RT; external beam or brachytherapy) is an option for men with low-risk disease not suitable for active surveillance (III, B).
  - RP or RT (external beam or brachytherapy) is recommended for men with intermediate-risk disease (I, B).
  - Primary ADT alone is not recommended as standard initial treatment for the non-metastatic disease (I, D).
  - External beam RT plus ADT is recommended for men with high-risk or locally advanced prostate cancer (I, B).
  - RP plus pelvic lymphadenectomy is an option for selected men with high-risk disease (III, B).
  - Men receiving radical RT for an intermediate-risk disease should have short-course ADT for 4–6 months (I, A).
  - Men receiving radical RT for the high-risk disease should have long-course ADT (18–36 months) (I, A).
  - Neoadjuvant docetaxel chemotherapy may be offered before RT for young, fit men with very high-risk localised prostate cancer (I, C).
  - Following RP, patients should have their serum prostate-specific antigen (PSA) level monitored, with salvage RT recommended in the event of PSA failure (III, B).
  - Adjuvant postoperative RT after RP is not routinely recommended (I, B).
  - Salvage RT should start early (e.g. PSA <0.5 ng/ml) (III, B). Concomitant ADT for 6 months or bicalutamide 150 mg daily for 2 years may be offered to men having salvage RT (I, B).
  - Men having salvage RT to the prostate bed may be offered pelvic nodal RT (I, C).
  - Men with biochemical relapse after radical RT who may be candidates for local salvage or metastasis-directed treatment should undergo imaging with PET-CT (III, B).
  - Early ADT alone is not recommended for men with biochemical relapse unless they have a rapid PSA doubling time, symptomatic local disease or proven metastases (II, D).
  - Men starting ADT for biochemical relapse, in the absence of metastatic disease, should be offered intermittent rather than continuous treatment (I, B).

Metastatic CRPC

- Recommendations:
  - Abiraterone or enzalutamide (ESMO-MCBS v1.1 scores: 4) is recommended for asymptomatic/mildly symptomatic men with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC) (I, A).
  - Docetaxel (ESMO-MCBS v1.1 score: 4) is recommended for men with mCRPC (I, A).
  - In patients with mCRPC in the post-docetaxel setting, abiraterone (ESMO-MCBS v1.1 score: 4), enzalutamide (ESMO-MCBS v1.1 score: 4) and cabazitaxel (ESMO-MCBS v1.1 score: 3) are recommended options (I, A).
  - In patients with bone metastases from CRPC at risk for clinically significant skeletal-related events, a bisphosphonate or denosumab is recommended (I, B).
  - 223Ra (ESMO-MCBS v1.1 score: 5) is recommended for men with bone-predominant, symptomatic mCRPC without visceral metastases (I, B).

- 223Ra is not recommended in combination with abiraterone and prednisolone (I, E).
- The use of a second AR inhibitor (abiraterone after enzalutamide or vice versa) is not recommended (II, D).

Regulatory status

EMA [2]	FDA [4]
Approval status for this indication: On 16 September 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Firmagon®. The CHMP adopted an extension to the existing indication as follows: ❖ Firmagon is a GnRH antagonist indicated as a neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone-dependent prostate cancer. ❖ Firmagon is GnRH antagonist indicated for the treatment of high-risk localised and locally advanced hormone-dependent prostate cancer in combination with radiotherapy (*for further information regarding this indication, please see Oncology Fact Sheet Nr. 66, available at https://aihta.at/page/horizon-scanning-in-der-onkologie-berichte/de*). **Other indications**: Firmagon® is indicated ❖ for treatment of adult male patients with advanced hormone-dependent prostate cancer.	**Approval status for this indication**: not approved **Other indications**: ❖ Firmagon® is indicated for the treatment of patients with advanced prostate cancer.

Costs [5]

Firmagon® 80 mg powder and solvent for solution for injection = € 150.00 (ex-factory price)

Special warnings and precautions for use [1]

- **Effect on QT/QTc interval**
  - Long-term androgen deprivation therapy may prolong the QT interval.
  - Firmagon® has not been studied in patients with a history of a corrected QT interval over 450 msec, in patients with a history of or risk factors for torsades de pointes and in patients receiving concomitant medicinal products that might prolong the QT interval. Therefore, in such patients, the benefit/risk ratio of Firmagon® must be thoroughly appraised.
  - A thorough QT study showed that there was no intrinsic effect of degarelix on QT/QTc interval.
- **Hepatic impairment**
  - Patients with known or suspected hepatic disorder have not been included in long-term clinical trials with degarelix.
  - Mild, transient increases in ALT and AST have been seen, these were not accompanied by a rise in bilirubin or clinical symptoms.
  - Monitoring of liver function in patients with a known or suspected hepatic disorder is advised during treatment.
  - The pharmacokinetics of degarelix has been investigated after single intravenous administration in subjects with mild to moderate hepatic impairment.
- **Renal impairment**
  - Degarelix has not been studied in patients with severe renal impairment and caution is therefore warranted.
- **Hypersensitivity**
  - Degarelix has not been studied in patients with a history of severe untreated asthma, anaphylactic reactions or severe urticaria or angioedema.
- **Changes in bone density**
  - Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist.
  - It can be anticipated that long periods of testosterone suppression in men will have effects on bone density.
  - Bone density has not been measured during treatment with degarelix.
- **Glucose tolerance**
  - A reduction in glucose tolerance has been observed in men who have had orchiectomy or who have been treated with a GnRH agonist.
  - Development or aggravation of diabetes may occur; therefore diabetic patients may require more frequent monitoring of blood glucose when receiving androgen deprivation therapy.

- The effect of degarelix on insulin and glucose levels has not been studied.

❖ **Cardiovascular disease**

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

Effect on of degarelix on prostate volume, disease-related mortality and increased disease free survival [1][1]

❖ Neo-adjuvant androgen deprivation therapy prior to radiotherapy has been shown to impact prostate volume reduction, reduced disease related mortality and increased disease free survival in patients with high-risk localised or locally advanced prostate cancer (RTOG 86-10, TROG 96-01, RTOG 92-02, and Mason M et al. Clinical Oncology 2013).

❖ In a randomised parallel-arm, active-controlled, open-label trial, conducted in 244 men with a UICC prostate cancer TNM category T2 (b or c)/T_3/T_4, No, Mo, Gleason score >7, or prostate specific antigen >10ng/mL and a total prostate volume >30, three months therapy with degarelix (240/80 mg dose regimen) resulted in a 37% reduction in prostate volume as measured by trans-rectal ultrasound scan in patients requiring hormonal therapy prior to radiotherapy and in patients who were candidates for medical castration. The prostate volume reduction was similar to that attained with goserelin plus anti-androgen protection (Mason M et al. Clinical Oncology 2013).

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Abbreviations: ADT=androgen deprivation therapy, AE=adverse event, ALT=alanine transaminase, AST=aspartate aminotransferase, 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, FSH=follicle stimulating hormone, GnRH=gonadotrophin releasing-hormone, HR=hazard ratio, I=intervention, LH= luteinizing hormone, mCRPC=metastatic castration-resistant prostate cancer, n=number of patients, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PSA=prostate-specific antigen, QoL=quality of life, RP=radical prostatectomy, RT=radiotherapy, SAE=serious adverse event, IUCC=Union for International Cancer Control

References:

1. European Medicines Agency (EMA). Firmagon: EPAR - Product Information [Available from: https://www.ema.europa.eu/en/documents/product-information/firmagon-epar-product-information_en.pdf].
2. European Medicines Agency (EMA). Medicines. Firmagon. [Available from: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/firmagon].
3. Parker C, Castro E, Fizazi K, Heidenreich A, Ost P, Procopio G, et al. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020 Sep;31(9):1119-1134.
4. U.S. Food and Drug Administration (FDA). Firmagon. Label Information [Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022201s016lbl.pdf].
5. Österreichischer Apotheker-Verlag. Warenverzeichnis Online [Available from: https://warenverzeichnis.apoverlag.at/].

[1] *No current approval study could be identified for this indication. Thus, information regarding the effect of degarelix as a neo-adjuvant treatment prior to radiotherapy was extracted from the EPAR product information.*