HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

23 September 2009

FIRMAGON 80 mg, powder and solvent for solution for injection
B/1 (CIP: 394 326-8)

FIRMAGON 120 mg, powder and solvent for solution for injection
B/2 (CIP: 394 327-4)

Applicant: FERRING SAS

Degarelix

List I

ATC Code: L02BX02

Date of marketing authorisation (European centralised procedure): 17 February 2009

Reason for request: inclusion on list of products reimbursed by National Insurance and for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance

Degarelix

1.2. Background

Degarelix is a selective gonadotrophin releasing hormone (GnRH) antagonist. It 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 (T) by the testes.

1.3. Indication

"FIRMAGON is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer."

1.4. Dosage

"Starting dose	**Maintenance dose – monthly administration**
240 mg administered as two subcutaneous injections of 120 mg each	80 mg administered as one subcutaneous injection

The first maintenance dose should be given one month after the starting dose."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

L	Antineoplastic and immunomodulating agents
L02	Endocrine therapy
L02B	Hormone antagonists and related agents
L02BX	Other hormone antagonists and related agents
L02BX02	degarelix

2.2. Medicines in the same therapeutic category

Comparator medicines
None

2.3. Medicines with a similar therapeutic aim

Comparator medicines

- GnRH analogues indicated in the treatment of advanced prostate cancer:

Leuprorelin:

- ENANTONE SR 3.75 mg, powder and solvent for suspension for injection (SC or IM), prolonged release
- ENANTONE SR 11.25 mg, microspheres and solution for parenteral use (SC or IM), prolonged release

Indicated in the treatment of advanced hormone-dependent prostate cancer.

- ELIGARD (7.5 mg, 22.5 mg and 45 mg), powder and solvent for solution for injection

Indicated in the treatment of advanced hormone-dependent prostate cancer.

Goserelin:

- ZOLADEX 10.8 mg, implant in pre-filled syringe for subcutaneous use
- ZOLADEX 3.6 mg, implant in pre-filled syringe for subcutaneous use

Indicated as an adjuvant treatment with external radiotherapy in locally advanced prostate cancer (stage T3 - T4 on TMN classification, or stage C of the AUA classification).

Triptorelin:

- GONAPEPTYL 3.75 mg, powder and solvent for suspension for injection, prolonged release, in pre-filled syringes

Indicated in the treatment of advanced hormone-dependent prostate cancer.

- DECAPEPTYL SR 11.25 mg, powder and solvent for suspension for injection (IM), prolonged-release form over 3 months
- DECAPEPTYL SR 3 mg, powder and solvent for suspension for injection (IM), prolonged-release form over 28 days

Indicated in the treatment of locally advanced or metastatic prostate cancer.

- Anti-androgens indicated in prostate cancer:

- CASODEX (bicalutamide)
- ANANDRON (nilutamide)
- EULEXIN (flutamide)
- ANDROCUR (cyproterone)

3. ANALYSIS OF AVAILABLE DATA

The submitted dossier consists of:
- five phase II non-comparative studies, the aim of which was to determine the efficacy and optimal treatment regimen. Details of these studies will therefore not be given in this opinion.
- one phase III comparative study versus leuprorelin. Following this study, a post-hoc analysis of progression-free survival (time to PSA escape and death) was carried out. Because of the chosen methodology, this analysis will not be taken into account in this opinion.

3.1. Efficacy

Non-inferiority study of two doses of subcutaneous degarelix (an initial dose of 240 mg followed by monthly doses of 160 mg or 80 mg) versus leuprorelin 7.5 mg given intramuscularly in 620 patients with prostate cancer requiring androgen suppression.
Statistical analysis was based on the following hypothesis: non-inferiority was established if the lower limit of the 97.5% confidence interval of the differences between percentages of castration (blood testosterone ≤ 0.5 ng/mL from day 28 to day 364) for both treatments (degarelix versus leuprorelin) was less than 10% in absolute values.

Primary endpoint: percentage of patients achieving blood testosterone ≤ 0.5 ng/mL after one year of treatment (from day 28 through to day 364).

Secondary endpoints:
- percentage of patients with increased blood testosterone during the first two weeks of treatment;
- percentage of patients with blood testosterone ≤ 0.5 ng/mL on day 3;
- percentage of patients with a reduction in prostate-specific antigen (PSA).

Results:
Of the 610 patients treated,
• 31% had localised prostate cancer;
• 29% had locally advanced prostate cancer;
• 20% had metastatic prostate cancer;
• 7% had disease of unknown metastatic status;
• 13% had previously undergone surgery or radiotherapy with curative intent and had increased PSA.
Median age was 74 years (range: 47-98).

Table I: percentage of patients achieving blood testosterone < 0.5 ng/mL after one year of treatment (ITT results).

	Degarelix 160 mg (n=202)	**Degarelix 80 mg** (n=207)	**leuprorelin 7.5 mg** (n=201)
Patients with blood testosterone < 0.5 ng/mL	199/202 (98.3%)	202/207 (97.2%)	194/201 (96.4%)
95% CI (%)	[94.8 - 99.4]	[93.5 - 98.8]	[92.5 - 98.2]
Absolute difference FIRMAGON vs leuprorelin	1.9%	0.9%	
97.5% CI (%)	[-1.8 - 5.7]	[-3.2 - 5.0]	
p non-inferiority	<0.05	<0.05	

ITT results for the primary endpoint demonstrated that FIRMAGON was non-inferior to leuprorelin 7.5 mg. Similar results were observed for the per-protocol analysis.

Table 2: Percentage of patients with blood testosterone ≤ 0.5 ng/mL after initiation of treatment.

Time	**Degarelix** 80 mg SC	**Leuprorelin** 7.5 mg IM
Day 1	52%	0%
Day 3	96%	0%
Day 7	99%	1%
Day 14	100%	18%
Day 28	100%	100%

The percentage of patients with blood testosterone ≤ 0.5 ng/mL on day 3 was 96% in the FIRMAGON arm vs none in the leuprorelin arm.

Levels of prostate-specific antigen (PSA) had reduced by 64% two weeks after administration of degarelix, by 85% after 1 month, and by 95% after 3 months and PSA reduction (around 97%) was maintained throughout the treatment duration (1 year) .

The percentage of patients with an increase in blood testosterone during the first 2 weeks of treatment was 80.1% in the leuprorelin arm and 0% in the FIRMAGON arm. The number of patients who received an anti-androgen in combination with the study treatments was 23 (11%) in the leuprorelin arm and 4 in the FIRMAGON arm. Complete androgen blockade is recommended during the first month of LH-RH analogue treatment, in order to limit the risk of flare-up[1] during the initial phase of treatment.
The monthly dose of 80 mg after a loading dose of 240 mg is the dosage contained in the marketing authorisation.

3.2. Adverse effects

The most commonly observed adverse events during degarelix treatment in the pivotal phase III study were hot flushes (25%) and weight gain (7%), in addition to injection site reactions.
According to the SPC anti-degarelix antibodies were observed to appear in 10% of patients during a one-year course of FIRMAGON treatment. There was no observed correlation between emergence of these antibodies and the efficacy and safety of FIRMAGON after one year of treatment. Beyond one year, there are no efficacy or safety data relating to the emergence of antibodies.
There are no long-term safety data for this product.

3.3. Conclusion

In a comparative study of 620 patients with prostate cancer requiring androgen suppression therapy, it was shown that FIRMAGON was non-inferior to leuprorelin in terms of percentage of patients achieving blood testosterone ≤ 0.5 ng/mL after one year treatment.
The percentage of patients with an increase in blood testosterone during the first 2 weeks of treatment was 80.1% in the leuprorelin arm and 0% in the FIRMAGON arm.
The Committee emphasises that, in conversely to the recommended practice in France, the combination of an antiandrogen and a GnRH analogue during the first month of treatment was prescribed only in 11 % of patients in the comparator group..
There are no clinical data demonstrating the benefits of this product in the treatment of prostate cancer in comparison with Gn-RH analogues. Results of a post-hoc analysis on progression-free survival could not be considered.

[1] Worsening of symptoms linked to raised blood testosterone

The safety profiles of the two treatments were similar, apart from the emergence of anti-degarelix antibodies.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Prostate cancer is a life-threatening condition;
These products are intended to provide curative treatment;
The efficacy/adverse effects ratio is high;
This is a first- or second-line treatment;
There are alternative medicinal products available;

Public health benefit:

Prostate cancer is the commonest cancer. In terms of mortality, it is the 4th highest cause of death by cancer in men .

The burden represented by prostate cancer is significant. The burden corresponding to the population falling under the therapeutic indication for FIRMAGON (advanced hormone-dependent prostate cancer) is moderate.

Improved management of cancer is a public health need coming within the scope of identified priorities (Public health law 2004). However, FIRMAGON does not provide any additional response to this public health need in comparison with the current strategy.

Given the available clinical data and existing therapeutic strategies, FIRMAGON is not expected to have an impact on morbidity and mortality. In addition, FIRMAGON has not been shown to provide any improvement in quality of life of treated patients.

It remains to be seen whether the results of the pivotal study can be transposed into clinical practice, given the limited duration of the study (12 months).

As a result, FIRMAGON is not expected to benefit public health.

The actual benefit of FIRMAGON is substantial.

4.2. Improvement in actual benefit

In the context of the current strategy for treatment of advanced prostate cancer, with a combination of a Gn-RH analogue and an antiandrogen in the first month of treatment, FIRMAGON provides no improvement in actual benefit (IAB level V).

4.3. Therapeutic use[2]

"Locally advanced cancer (T3/T4, N0-x, M0)
The gold standard treatment of locally advanced cancers (T3/T4, N0-x, M0) consists of conformal radiotherapy from the prostatic capsule up to the pelvic lymph nodes with or without intensity modulation with hormone therapy lasting 3 years.
For a restricted group of patients (T3, young men, functional urinary signs, low risk of metastasis), radical prostatectomy with no preservation of erectile nerves is an option. This must meet strict quality criteria and must be preceded by lymph node dissection. There is no benefit in giving hormone treatment before total prostatectomy. The patient is informed of the possibility of complementary adjuvant treatment (radiotherapy and/or hormone therapy) depending on the results of histological examination of the operative specimen.

Prostate cancer with pelvic lymph node involvement (all T stages, cN1/pN1, M0)
Early and long-term hormone therapy is the gold-standard treatment. Total prostatectomy can be discussed if lymph node involvement is limited to 2 lymph nodes or less and is microscopic.
External radiotherapy of the prostatic capsule and pelvis can be offered. The "watchful waiting" principle involves postponing hormone treatment until urinary and bone symptoms develop, or until total PSA increases rapidly. This is possible with hormone treatment (or indeed a combination of hormone and radiotherapy) that is postponed for an asymptomatic patient with an estimated life expectancy (taking into account age and comorbidities) of less than 10 years.

Metastatic prostate cancer
Hormone therapy is the gold-standard treatment, using the following procedures:
- early initiation of treatment
- combination of LHRH analogue and anti-androgen during the first month of treatment
- followed by recommended monotherapy with LHRH analogue or surgical castration.

Complete long-term androgen blockade has no proven benefit. Intermittent hormone therapy and combined hormone therapy and chemotherapy are currently being evaluated.
Hormone resistant forms can require hormone manipulation (alteration to hormone therapy) or treatment with chemotherapy if bone pain from metastases occurs or general condition worsens, or if criteria for rapid disease progression are present.
Bisphosphonates given intravenously are part of protocols for prevention of bone complications (pathological fractures, spinal cord compression, bone irradiation or surgery, hypercalcaemia caused by tumours) of some advanced malignant tumours (including prostate cancer) with bone involvement.
Watchful waiting is possible for an asymptomatic patient with an estimated life expectancy (taking into account age and comorbidities) of less than 10 years. Deferred hormone therapy is undertaken in cases of significant progression on clinical examination or laboratory parameters."

Given the available data, FIRMAGON, a GnRH antagonist given as a monotherapy, is an additional therapeutic agent in hormone therapy for advanced prostate cancer.

[2] ALD (long-term conditions) guide "Prostate cancer": www.has-sante.fr. September 2008

4.4. Target Population

The target population for FIRMAGON is represented by patients with locally advanced (T3 and T4) or metastatic prostate cancer.

In France, the incidence of prostate cancer was estimated to be approximately 62,000 cases in 2005[3].
According to data from a sample of 5 of the 8 French cancer registries, of the 1000 patients diagnosed with prostate cancer in 1995, 18%[4] had with locally advanced disease (T3 or T4). The number of new cases of locally advanced prostate cancer would therefore appear to be around 11,200 per year. Conversely,

- it is not known what proportion of patients require single hormone therapy .
- there are no available epidemiological data that would enable an assessment of the proportion of patients initially diagnosed with localised disease (T1, T2, N0) and who progress to locally advanced disease.

Metastatic disease represents 20% of incident cases of prostate cancer, or around 12,400 patients per year.

On the basis of these data, the target population for FIRMAGON is estimated to be 24,000 patients per year.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicinal products approved for use by hospitals and various public services in the indication and at the dosage given in the marketing authorisation.

4.5.1 Packaging: Appropriate for the prescription conditions

4.5.2 Reimbursement rate: 100%

[3] InVS, HCL, Francim, INCa: Presentation of latest cancer incidence and mortality data for France, and trends over the last 25 years (1980-2005) - Press conference, 21 February 2008.
[4] Bauvin E, Soulié M, Ménégoz F, Macé-Lesec'h J, Buémi A, Velten M, Villers A, Grosclaude P. Medical and non-medical determinants of prostate cancer management: a population-based study. Eur J Cancer. 2003 Nov;39(16):2364-71