FIRMAGON® 120mg

Powder and solvent for solution for injection

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 120 mg degarelix (as acetate). After reconstitution, each ml solution contains 40 mg of degarelix.

List of excipients:
Powder: Mannitol (E421).
Solvent: Water for injections.

PHARMACEUTICAL FORM

Powder and solvent for solution for injection
Powder: White to off-white powder.
Solvent: Clear, colourless solution.

THERAPEUTIC INDICATIONS

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

POSOLOGY AND METHOD OF ADMINISTRATION

Posology

Starting dose	Maintenance dose – monthly administration
240 mg administered as two consecutive 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.

The therapeutic effect of degarelix should be monitored by clinical parameters and prostate specific antigen (PSA) serum levels. Clinical studies have shown that testosterone (T) suppression occurs immediately after administration of the starting dose with 96% of the patients having serum testosterone levels corresponding to medical castration (T≤0.5 ng/ml) after three days and 100% after one month. Long term treatment with the maintenance dose up to 1 year shows that 97% of the patients have sustained suppressed testosterone levels (T≤0.5 ng/ml).

In case the patient's clinical response appears to be sub-optimal, it should be confirmed that serum testosterone levels are remaining sufficiently suppressed.
Since degarelix does not induce a testosterone surge it is not necessary to add an anti-androgen as surge protection at initiation of therapy**.**

Method of administration
FIRMAGON® must be reconstituted prior to administration. For instructions on reconstitution and administration, please see section Instructions For Use.

FIRMAGON® is for subcutaneous use ONLY, not to be administered intravenously.
Intramuscular administration is not recommended as it has not been studied.

FIRMAGON® is administered as a subcutaneous injection in the abdominal region. The injection site should vary periodically. Injections should be given in areas where the patient will not be exposed to pressure e.g. not close to waistband or belt and not close to the ribs.

Special patient populations
Elderly, hepatically or renally impaired patients:
There is no need to adjust the dose for the elderly or in patients with mild or moderate liver or kidney function impairment (see section Pharmacokinetic Properties). Patients with severe liver or kidney impairment have not been studied and caution is therefore warranted (see section Special Warnings and Precautions for Use).

There is no relevant indication for use of FIRMAGON® in women, children and adolescents.

INSTRUCTIONS FOR USE

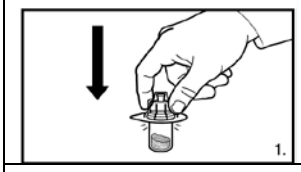
The instructions for reconstitution must be followed carefully.

Administration of other concentrations is not recommended because the gel depot formation is influenced by the concentration. The reconstituted solution should be a clear liquid, free of undissolved matter.

NOTE:

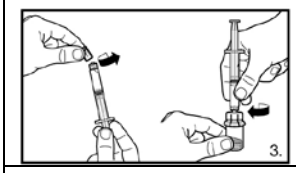
• THE VIALS SHOULD NOT BE SHAKEN

The pack contains two vials of powder and two pre-filled syringes with solvent that must be prepared for subcutaneous injection. Hence, the procedure described below need to be repeated a second time.

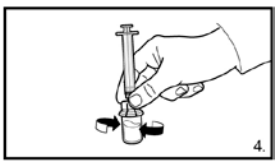


1. Remove the cover from the vial adapter pack. Attach the adapter to the powder vial by pressing the adapter down until the spike pushes through the rubber stopper and the adapter snaps in place.

2. Prepare the pre-filled syringe by attaching the plunger rod.

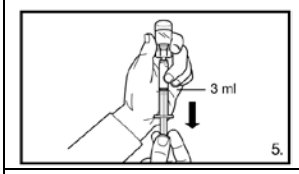


3. Remove the cap of the pre-filled syringe. Attach the syringe to the powder vial by screwing it on to the adapter. **Transfer all solvent to the powder vial.**



4. With the syringe still attached to the adapter, swirl gently until the liquid looks clear and without undissolved powder or particles. If the powder adheres to the side of the vial above the liquid surface, the vial can be tilted slightly. **Avoid shaking to prevent foam formation.**

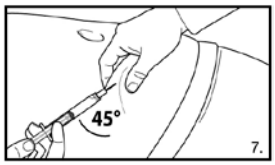
A ring of small air bubbles on the surface of the liquid is acceptable. The reconstitution procedure usually takes a few minutes, but may take up to 15 minutes in some cases.



5. Turn the vial upside down and draw up to the line mark on the syringe for injection.

Always make sure to withdraw the precise volume and adjust for any air bubbles**.**

6. Detach the syringe from the vial adapter and attach the needle for deep subcutaneous injection to the syringe.



7. Perform a deep subcutaneous injection. To do so: grasp the skin of the abdomen, elevate the subcutaneous tissue and insert the needle deeply at an angle of **not less than 45 degrees.**

Inject **3 ml of FIRMAGON® 120 mg** slowly, immediately after reconstitution*.

8. No injections should be given in areas where the patient will be exposed to pressure, e.g. around the belt or waistband or close to the ribs.

Do not inject directly into a vein. Gently pull back the plunger to check if blood is aspirated. If blood appears in the syringe, the medicinal product can no longer be used. Discontinue the procedure and discard the syringe and the needle (reconstitute a new dose for the patient).

9. Repeat the reconstitution procedure for the second dose. Choose a different injection site **and inject 3 ml.**

* Chemical and physical in-use stability has been demonstrated for 2 hours at 25ºC. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

No special requirements for disposal.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Effect on QT/QTc interval
Long-term androgen deprivation therapy may prolong the QT interval. In the confirmatory study comparing FIRMAGON® to leuprorelin periodic (monthly) ECGs were performed; both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients, and 500 msec in 1% and 2% of the degarelix and leuprorelin patients, respectively (see section Pharmacodynamic Properties).
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 (see sections Interaction with Other Medicinal Products and Other Forms of Interactions and Undesirable Effects).
A thorough QT study in healthy men showed that there was no intrinsic effect of degarelix on QT/QTc interval (see section Undesirable Effects).

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 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 (see section Pharmacokinetic Properties).

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
No formal drug-drug interaction studies have been performed.

Since androgen deprivation treatment may prolong the QTc interval, the concomitant use of degarelix with medicinal products known to prolong the QTc interval or medicinal products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, cisapride, moxifloxacine, antipsychotics, etc. should be carefully evaluated (see section Special Warnings and Precautions for Use).

Degarelix is not a substrate for the human CYP450 system and has not been shown to induce or inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 to any great extent *in vitro*. Therefore, clinically significant pharmacokinetic drug-drug interactions in metabolism related to these isoenzymes are unlikely.

FERTILITY, PREGNANCY AND LACTATION

Pregnancy and breast-feeding

There is no relevant indication for use of FIRMAGON® in women.

Fertility

FIRMAGON® may inhibit male fertility as long as the testosterone is suppressed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

FIRMAGON® has no or negligible influence on the ability to drive and use machines. Fatigue and dizziness are common adverse reactions that might influence the ability to drive and use machines.

UNDESIRABLE EFFECTS

The most commonly observed adverse reactions during degarelix therapy in the confirmatory phase III study (N=409) were due to the expected physiological effects of testosterone suppression, including hot flushes and weight increase (reported in 25% and 7%, respectively, of patients receiving treatment for one year), or injection site adverse events. Transient chills, fever or influenza like illness were reported to occur hours after dosing (in 3%, 2% and 1% of patients, respectively).

The injection site adverse events reported were mainly pain and erythema, reported in 28% and 17% of patients, respectively, less frequently reported were swelling (6%), induration (4%) and nodule (3%). These events occurred primarily with the starting dose whereas during maintenance therapy with the 80 mg dose, the incidence of these events per 100 injections was: 3 for pain and <1 for erythema, swelling, nodule and induration. The reported events were mostly transient, of mild to moderate intensity and led to very few discontinuations (<1%). Serious injection site reactions were very rarely reported such as injection site infection, injection site abscess or injection site necrosis that could require surgical treatment/drainage.

The frequency of undesirable effects listed below is defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Frequency of adverse drug reactions reported in 1259 patients treated for a total of 1781 patient years (phase II and III studies) and from post-marketing reports.

MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders		Anaemia*		Neutropenic fever
Immune system disorders			Hypersensitivity	Anaphylactic reactions
Metabolism and nutrition disorders		Weight increase*	Hyperglycemia/Diabetes mellitus, cholesterol increased, weight decreased, appetite decreased, changes in blood calcium	
Psychiatric disorders		Insomnia	Depression, libido decreased*	
Nervous system disorders		Dizziness, headache	Mental impairment, hypoaesthesia	
Eye disorders			Vision blurred	

Cardiac disorders			Cardiac arrhythmia (incl. atrial fibrillation), palpitations, QT prolongation*(see sections Special Warnings and Precautions for Use and Interaction with Other Medicinal Products and Other Forms of Interaction)	Myocardial infarction, cardiac failure
Vascular disorders	Hot flush*		Hypertension, vasovagal reaction (incl. hypotension)	
Respiratory, thoracic and mediastinal disorders			Dyspnoea	
Gastrointestinal disorders		Diarrhoea, nausea	Constipation, vomiting, abdominal pain, abdominal discomfort, dry mouth	
Hepatobiliary disorders		Liver transaminases increased	Bilirubin increased, alkaline phosphatase increased	
Skin and subcutaneous tissue disorders		Hyperhidrosis (incl. night sweats)*, rash	Urticaria, skin nodule, alopecia, pruritus, erythema	
Musculoskeletal, connective tissue and bone disorders		Musculoskeletal pain and discomfort	Osteoporosis/osteopenia, arthralgia muscular weakness, muscle spasms, joint swelling/stiffness	
Renal and urinary disorders			Pollakiuria, micturition urgency, dysuria, nocturia, renal impairment, incontinence	
Reproductive system and breast disorders		Gynaecomastia*, testicular atrophy*, erectile dysfunction*	Testicular pain, breast pain, pelvic pain, genital irritation, ejaculation failure	
General disorders and administration site conditions	Injection site adverse reactions	Chills, pyrexia, fatigue*, Influenza-like illness	Malaise, peripheral oedema	

*Known physiological consequence of testosterone suppression

Changes in laboratory parameters

Changes in laboratory values seen during one year of treatment in the confirmatory phase III study (N=409) were in the same range for degarelix and a GnRH-agonist (leuprorelin) used as comparator. Markedly abnormal (>3*ULN) liver transaminase values (ALT, AST and GGT) were seen in 2-6% of patients with normal values prior to treatment, following treatment with both medicinal products. Marked decrease in haematological values, hematocrit (≤0.37) and hemoglobin (≤115 g/l) were seen in 40% and 13-15%, respectively, of patients with normal values prior to treatment, following treatment with both medicinal products. It is unknown to what extent this decrease in haematological values was caused by the underlying prostate cancer and to what extent it was a consequence of androgen deprivation therapy. Markedly abnormal values of potassium (≥5.8 mmol/l), creatinine (≥177 µmol/l) and BUN (≥10.7 mmol/l) in patients with normal values prior to treatment, were seen in 6%, 2% and 15% of degarelix treated patients and 3%, 2% and 14% of leuprorelin treated patients, respectively.

Changes in ECG measurements

Changes in ECG measurements seen during one year of treatment in the confirmatory phase III study (N=409) were in the same range for degarelix and a GnRH-agonist (leuprorelin) used as comparator.

Three (<1%) out of 409 patients in the degarelix group and four (2%) out of 201 patients in the leuprorelin 7.5 mg group, had a QTcF ≥ 500 msec. From baseline to end of study the median change in QTcF for degarelix was 12.0 msec and for leuprorelin was 16.7 msec.
The lack of intrinsic effect of degarelix on cardiac repolarisation (QTcF), heart rate, AV conduction, cardiac depolarisation, or T or U wave morphology was confirmed in a thorough QT study in healthy subjects (N=80) receiving an i.v. infusion of degarelix over 60 min, reaching a mean C_{max} of 222 ng/mL, approx. 3-4-fold the C_{max} obtained during prostate cancer treatment.

OVERDOSE
There is no clinical experience with the effects of an acute overdose with degarelix. In the event of an overdose the patient should be monitored and appropriate supportive treatment should be given, if considered necessary.

PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: Endocrine therapy, Other hormones antagonists and related agents, ATC code: L02BX02

Degarelix 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 (T) by the testes. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that removes the source of androgen. Unlike GnRH agonists, GnRH antagonist do not induce a LH surge with subsequent testosterone surge/tumour stimulation and potential symptomatic flare after the initiation of treatment.

A single dose of 240 mg degarelix, followed by a monthly maintenance dose of 80 mg, rapidly causes a decrease in the concentrations of LH, FSH and subsequently testosterone. The plasma concentration of dihydrotestosterone (DHT) decreases in a similar manner to testosterone.

Degarelix is effective in achieving and maintaining testosterone suppression well below medical castration level of 0.5 ng/ml. Maintenance monthly dosing of 80 mg resulted in sustained testosterone suppression in 97% of patients for at least one year. No testosterone microsurges were observed after re-injection during degarelix treatment. Median testosterone levels after one year of treatment were 0.087 ng/ml (interquartile range 0.06-0.15) N=167.

Results of the confirmatory Phase III study
The efficacy and safety of degarelix was evaluated in an open-label, multi-centre, randomised, active comparator controlled, parallel-group study. The study investigated the efficacy and safety of two different degarelix monthly dosing regimens with a starting dose of 240 mg (40 mg/ml) followed by monthly doses subcutaneous administration of 160 mg (40 mg/ml) or 80 mg (20 mg/ml), in comparison to monthly intramuscular administration of 7.5 mg leuprorelin in patients with prostate cancer requiring androgen deprivation therapy. In total 620 patients were randomised to one of the three treatment groups, of which 504 (81%) patients completed the study. In the degarelix 240/80 mg treatment group 41 (20%) patients discontinued the study, as compared to 32 (16%) patients in the leuprorelin group.

Of the 610 patients treated
• 31% had localised prostate cancer
• 29% had locally advanced prostate cancer
• 20% had metastatic prostate cancer
• 7% had an unknown metastatic status
• 13% had previous curative intent surgery or radiation and a rising PSA

Baseline demographics were similar between the arms. The median age was 74 years (range 47 to 98 years). The primary objective was to demonstrate that degarelix is effective with respect to achieving and maintaining testosterone suppression to below 0.5 ng/ml, during 12 months of treatment.
The lowest effective maintenance dose of 80 mg degarelix was chosen.

Attainment of serum testosterone (T) ≤0.5 ng/ml
FIRMAGON® is effective in achieving fast testosterone suppression, see Table 2.

Table 2: Percentage of patients attaining T≤0.5 ng/ml after start of treatment.

Time	Degarelix 240/80 mg	Leuprorelin 7.5 mg
Day 1	52%	0%

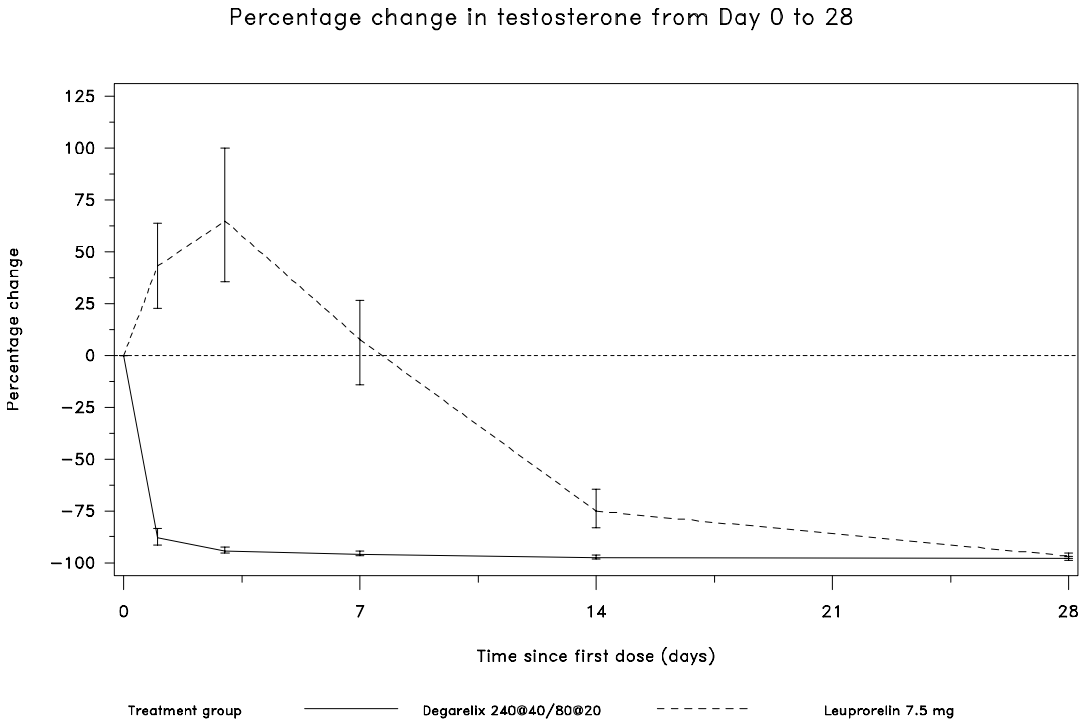
Day 3	96%	0%
Day 7	99%	1%
Day 14	100%	18%
Day 28	100%	100%

Avoidance of testosterone surge

Surge was defined as testosterone exceeding baseline by ≥15% within the first 2 weeks.

None of the degarelix-treated patients experienced a testosterone surge; there was an average decrease of 94% in testosterone at day 3. Most of the leuprorelin-treated patients experienced testosterone surge; there was an average increase of 65% in testosterone at day 3. This difference was statistically significant (p<0.001).

Figure 1: Percentage change in testosterone from baseline by treatment group until day 28 (median with interquartile ranges).



The primary end-point in the study was testosterone suppression rates after one year of treatment with degarelix or leuprorelin. The clinical benefit for degarelix compared to leuprorelin plus anti-androgen in the initial phase of treatment has not been demonstrated.

Testosterone Reversibility

In a study involving patients with rising PSA after localised therapy (mainly radical prostatectomy and radiation) were administered FIRMAGON® for seven months followed by a seven months monitoring period. The median time to testosterone recovery (>0.5 ng/mL, above castrate level) after discontinuation of treatment was 112 days (counted from start of monitoring period, i.e 28 days after last injection). The median time to testosterone >1.5 ng/mL (above lower limit of normal range) was 168 days.

Long-term effect

Successful response in the study was defined as attainment of medical castration at day 28 and maintenance through day 364 where no single testosterone concentration was greater than 0.5 ng/ml.

Table 3: Cumulative probability of testosterone ≤0.5 ng/ml from Day 28 to Day 364.

	Degarelix 240/80 mg N=207	Leuprorelin 7.5 mg N=201
No. of responders	202	194
Response Rate (confidence intervals)*	97.2% (93.5; 98.8%)	96.4% (92.5; 98.2%)

* Kaplan Meier estimates within group

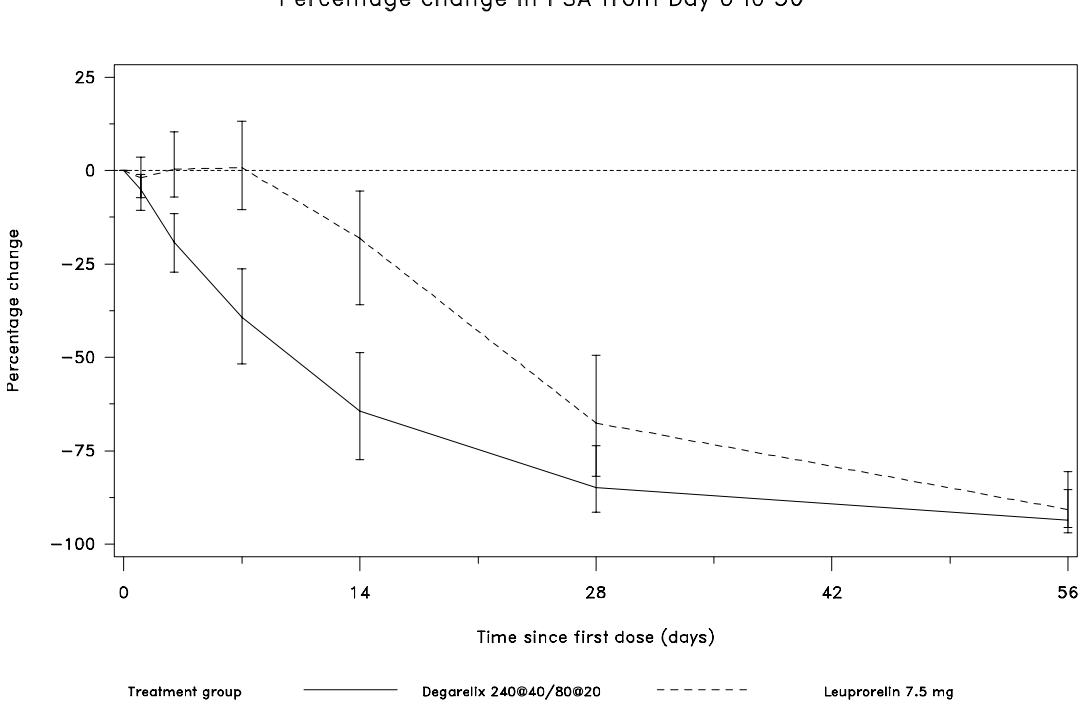
Attainment of prostate specific antigen (PSA) reduction

Tumour size was not measured directly during the clinical trial programme, but there was an indirect beneficial tumour response as shown by a 95% reduction after 12 months in median PSA for degarelix. The median PSA in the study at baseline was:

• for the degarelix 240/80 mg treatment group 19.8 ng/ml (interquartile range: P25 9.4 ng/ml, P75 46.4 ng/ml)

• for the leuprorelin 7.5 mg treatment group 17.4 ng/ml (interquartile range: P25 8.4 ng/ml, P75 56.5 ng/ml)

Figure 2: Percentage change in PSA from baseline by treatment group until day 56 (median with interquartile ranges).



This difference was statistically significant ($p<0.001$) for the pre-specified analysis at day 14 and day 28.

Prostate specific antigen (PSA) levels are lowered by 64% two weeks after administration of degarelix, 85% after one month, 95% after three months, and remained suppressed (approximately 97%) throughout the one year of treatment.

From day 56 to day 364 there were no significant differences between degarelix and the comparator in the percentage change from baseline.

Effect on prostate volume

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 (TRUS) 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.

Effect on QT/QTc intervals

In the confirmatory study comparing FIRMAGON® to leuprorelin periodic electrocardiograms were performed. Both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients. From baseline to end of study the median change for FIRMAGON® was 12.0 msec and for leuprorelin it was 16.7 msec.

Anti-degarelix antibody development has been observed in 10% of patients after treatment with FIRMAGON® for one year and 29% of patients after treatment with FIRMAGON® for up to 5.5 years. There is no indication that the efficacy or safety of FIRMAGON® treatment is affected by antibody formation after up to 5.5 years of treatment.

PHARMACOKINETIC PROPERTIES

Absorption

Following subcutaneous administration of 240 mg degarelix at a concentration of 40 mg/ml to prostate cancer patients in the pivotal study CS21, $AUC_{0\text{-}28\ days}$ was 635 (602-668) day*ng/ml, C_{max} was 66.0 (61.0-71.0) ng/ml and occurred at t_{max} at 40 (37-42) hours. Mean trough values were approximately 11-12 ng/ml after the starting dose and 11-16 ng/ml after maintenance dosing of 80 mg at a concentration of 20 mg/ml. Cmax degarelix plasma concentration decreases in a biphasic fashion, with a mean terminal half-life ($t_{½}$) of 29 days for the maintenance dose. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the depot formed at the injection site(s). The pharmacokinetic behavior of the medicinal product is influenced by its concentration in the solution for injection. Thus, C_{max} and bioavailability tend to decrease with increasing dose concentration while the half-life is increased. Therefore, no other dose concentrations than the recommended should be used.

Distribution
The distribution volume in healthy elderly men is approximately 1 l/kg. Plasma protein binding is estimated to be approximately 90%.

Biotransformation
Degarelix is subject to common peptidic degradation during the passage of the hepato-biliary system and is mainly excreted as peptide fragments in the faeces. No significant metabolites were detected in plasma samples after subcutaneous administration. *In vitro* studies have shown that degarelix is not a substrate for the human CYP450 system.

Elimination
In healthy men, approximately 20-30% of a single intravenously administered dose is excreted in the urine, suggesting that 70-80% is excreted via the hepato-biliary system. The clearance of degarelix when administered as single intravenous doses (0.864-49.4 µg/kg) in healthy elderly men was found to be 35-50 ml/h/kg.

Special populations
Patients with renal impairment
No pharmacokinetic studies in renally impaired patients have been conducted. Only about 20-30% of a given dose of degarelix is excreted unchanged by the kidneys. A population pharmacokinetics analysis of the data from the confirmatory Phase III study has demonstrated that the clearance of degarelix in patients with mild to moderate renal impairment is reduced by approximately 23%; therefore, dose adjustment in patients with mild or moderate renal impairment is not recommended. Data on patients with severe renal impairment is scarce and caution is therefore warranted in this patient population.

Patients with hepatic impairment
Degarelix has been investigated in a pharmacokinetic study in patients with mild to moderate hepatic impairment. No signs of increased exposure in the hepatically impaired subjects were observed compared to healthy subjects. Dose adjustment is not necessary in patients with mild or moderate hepatic impairment. Patients with severe hepatic dysfunction have not been studied and caution is therefore warranted in this group.

INCOMPATIBILITIES
In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

SHELF-LIFE
3 years

After reconstitution
Chemical and physical in-use stability has been demonstrated for 2 hours at 25ºC. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

STORAGE
Store below 30°C. Do not freeze.

PACKING SIZES
2 glass (type I) vials with bromobutyl stopper and aluminium flip-off seal containing 120 mg powder for solution for injection

2 pre-filled glass (type I) syringes with elastomer plunger stopper, tip cap and line-marking at 3 ml containing 3 ml solvent
2 plunger rods
2 vial adaptors
2 injection needles (25G 0.5 x 25 mm)

MANUFACTURER
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DATE OF REVISION
July 2016