ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FIRMAGON 80 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 80 mg degarelix (as acetate). After reconstitution, each ml of solution contains 20 mg of degarelix.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Powder: White to off-white powder
Solvent: Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 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**.**

Special 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 5.2). Patients with severe liver or kidney impairment have not been studied and caution is therefore warranted (see section 4.4).

Paediatric population
There is no relevant use of FIRMAGON in children and adolescents in the treatment of adult male patients with advanced hormone-dependent prostate cancer.

Method of administration
FIRMAGON must be reconstituted prior to administration. For instructions on reconstitution and administration, please see section 6.6.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.

4.4 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) electrocardiograms (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 5.1).
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 4.5 and 4.8).
A thorough QT study showed that there was no intrinsic effect of degarelix on QT/QTc interval (see section 4.8).

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 5.2).

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.

4.5 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, moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

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.

4.6 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.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile
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 reactions. 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 reactions 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 pr 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.

Tabulated list of adverse reactions

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 1,259 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 4.4 and 4.5)	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

Description of selected adverse reactions

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Other hormone antagonists and related agents, ATC code: L02BX02

Mechanism of action
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 antagonists 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 serum 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.

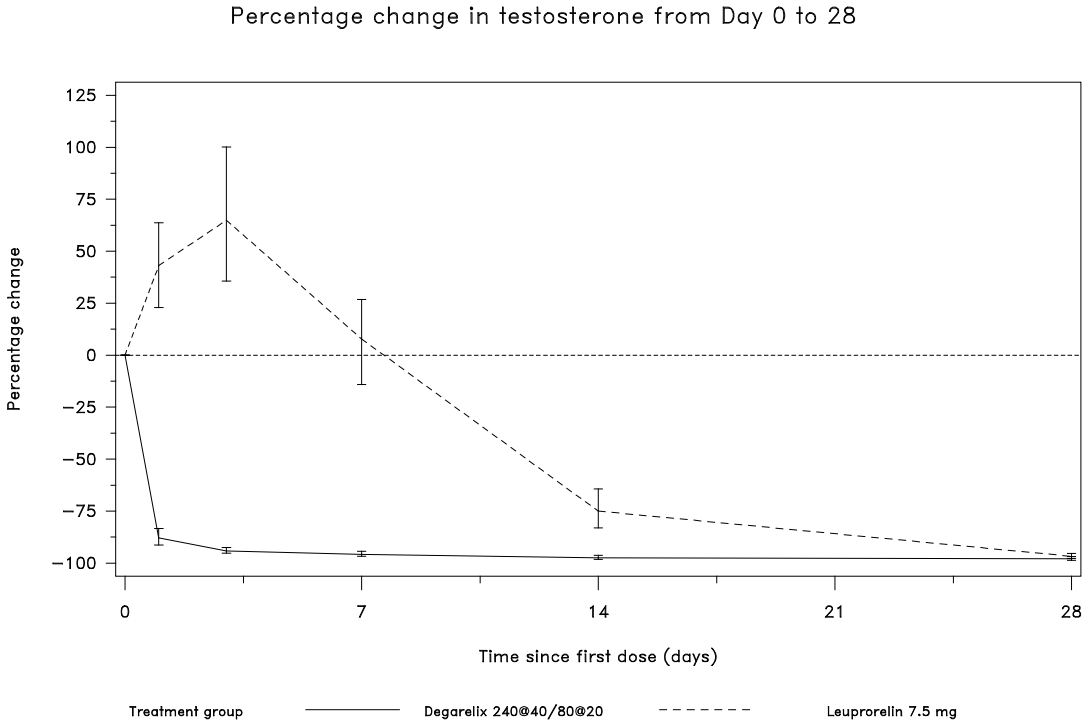
Time	Degarelix 240/80 mg	Leuprorelin 7.5 mg
Day 1	52%	0%
Day 3	96%	0%

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

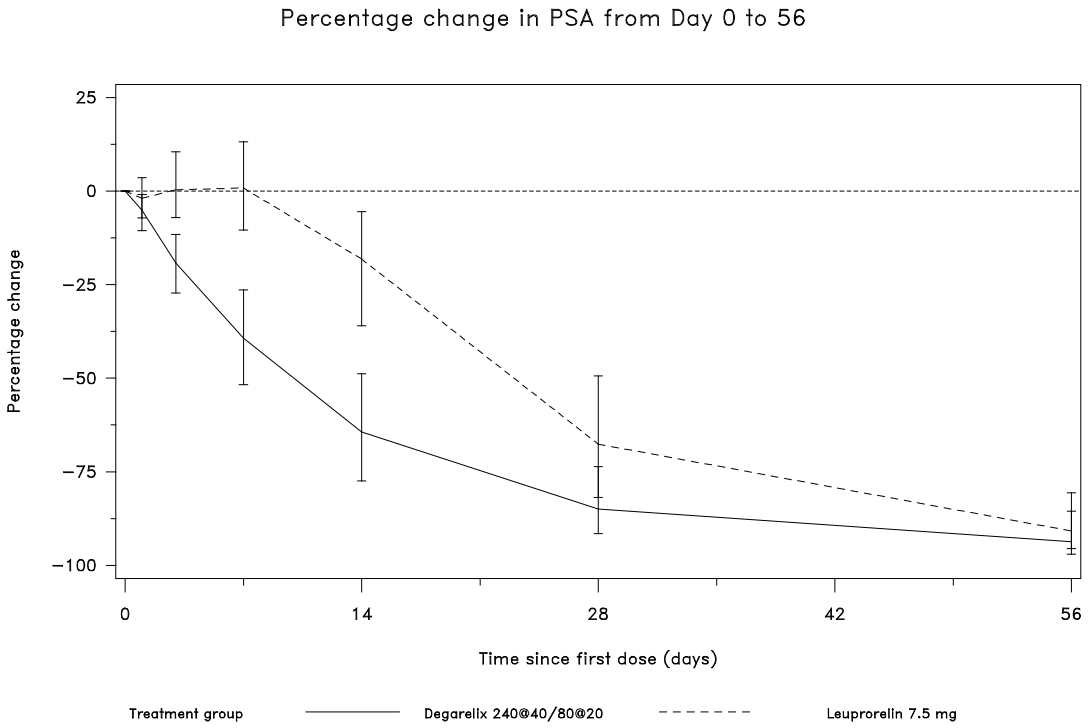
Attainment of prostate specific antigen (PSA) reduction

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 antibodies
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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with FIRMAGON in all subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 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. C_{max} 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.

5.3 Preclinical safety data

Animal reproduction studies showed that degarelix caused infertility in male animals. This is due to the pharmacological effect; and the effect was reversible.

In female reproduction toxicity studies degarelix revealed findings expected from the pharmacological properties. It caused a dosage dependent prolongation of the time to mating and to pregnancy, a reduced number of *corpora lutea*, and an increase in the number of pre- and post-implantation losses, abortions, early embryo/foetal deaths, premature deliveries and in the duration of parturition.

Preclinical studies on safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential revealed no special hazard for humans. Both *in vitro* and *in vivo* studies showed no signs of QT prolongation.

No target organ toxicity was observed from acute, subacute and chronic toxicity studies in rats and monkeys following subcutaneous administration of degarelix. Drug-related local irritation was noted in animals when degarelix was administered subcutaneously in high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Mannitol (E421)

Solvent
Water for injections

6.2 Incompatibilities

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

6.3 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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass (type I) vial with bromobutyl rubber stopper and aluminium flip-off seal containing 80 mg powder for solution for injection
Pre-filled glass (type I) syringe with elastomer plunger stopper, tip cap and line-marking at 4 ml containing 4.2 ml solvent
Plunger rod
Vial adapter
Injection needle (25G 0.5 x 25 mm)

Pack sizes
FIRMAGON is available in 2 pack-sizes:
Pack-size of 1 tray containing: 1 powder vial, 1 solvent pre-filled syringe, 1 plunger rod, 1 vial adapter and 1 needle.
Pack-size of 3 trays containing: 3 powder vials, 3 solvent pre-filled syringes, 3 plunger rods, 3 vial adapters and 3 needles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 one vial of powder and one pre-filled syringe with solvent that must be prepared for subcutaneous injection.

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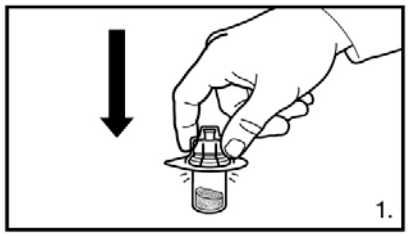
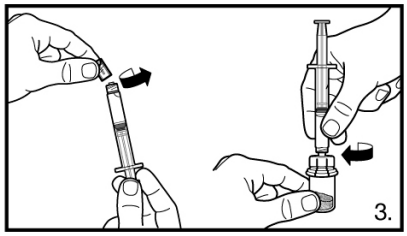
<tr><td> 
</td><td>1. Remove the cover from the vial adapter pack. Attach the adapter to the powder vial by pressing the adapter down until the spike pushes through the rubber stopper and the adapter snaps in place.</td></tr>
<tr><td colspan="2">2. Prepare the pre-filled syringe by attaching the plunger rod.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
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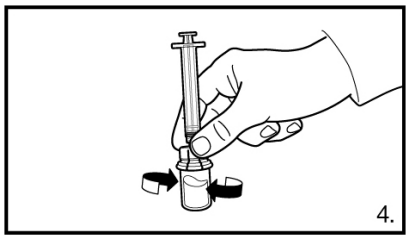
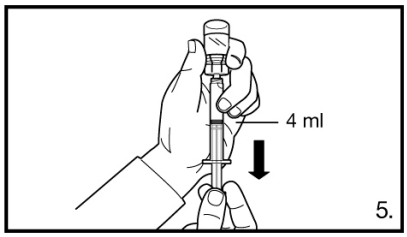
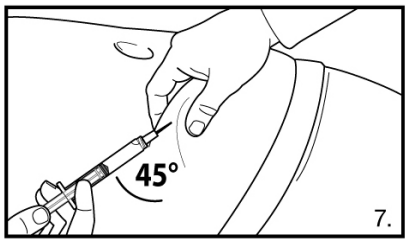
<tr><td> 
</td><td>4. With the syringe still attached to the adapter, swirl gently until the liquid looks clear and without undissolved powder or particles. If the powder adheres to the side of the vial above the liquid surface, the vial can be tilted slightly. Avoid shaking to prevent foam formation.

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.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
<tr><td colspan="2">6. Detach the syringe from the vial adapter and attach the needle for deep subcutaneous injection to the syringe.</td></tr>
<tr><td> 
</td><td>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 4 ml of FIRMAGON 80 mg slowly, immediately after reconstitution.</td></tr>
<tr><td colspan="2">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).</td></tr>
</table>

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
DK-2300 Copenhagen S
Denmark
Tel: +45 88 33 88 34

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/504/001

EU/1/08/504/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:17/02/2009
Date of latest renewal: 19/09/2013

10. DATE OF REVISION OF THE TEXT

{DD/MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

1. NAME OF THE MEDICINAL PRODUCT

FIRMAGON 120 mg powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Powder: White to off-white powder
Solvent: Clear, colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 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**.**

Special 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 5.2). Patients with severe liver or kidney impairment have not been studied and caution is therefore warranted (see section 4.4).

Paediatric population
There is no relevant use of FIRMAGON in children and adolescents in the treatment of adult male patients with advanced hormone-dependent prostate cancer.

Method of administration
FIRMAGON must be reconstituted prior to administration. For instructions on reconstitution and administration, please see section 6.6.

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.

4.4 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) electrocardiograms (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 5.1).
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 4.5 and 4.8).
A thorough QT study showed that there was no intrinsic effect of degarelix on QT/QTc interval (see section 4.8).

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 5.2).

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.

4.5 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, , moxifloxacin, antipsychotics, etc. should be carefully evaluated (see section 4.4).

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.

4.6 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.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile
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 reactions. 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 reactions 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 pr 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.

Tabulated list of adverse reactions

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 4.4 and 4.5)	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

Description of selected adverse reactions

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Endocrine therapy, Other hormone antagonists and related agents, ATC code: L02BX02

Mechanism of action
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 antagonists 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 serum 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.

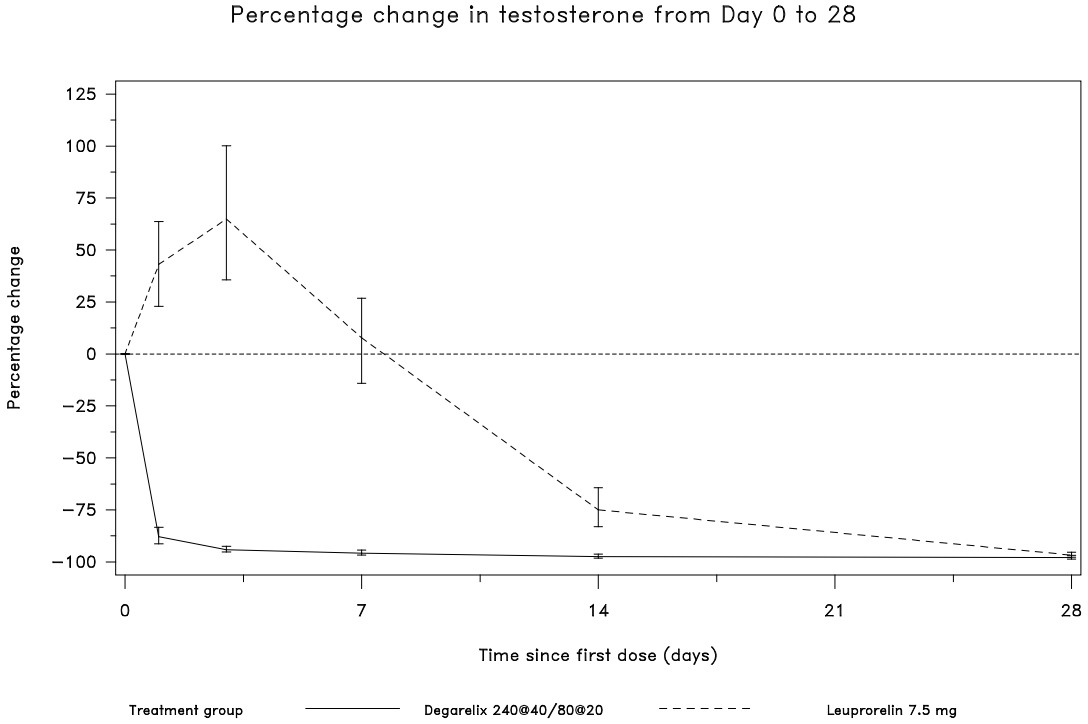
Time	Degarelix 240/80 mg	Leuprorelin 7.5 mg
Day 1	52%	0%
Day 3	96%	0%
Day 7	99%	1%

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

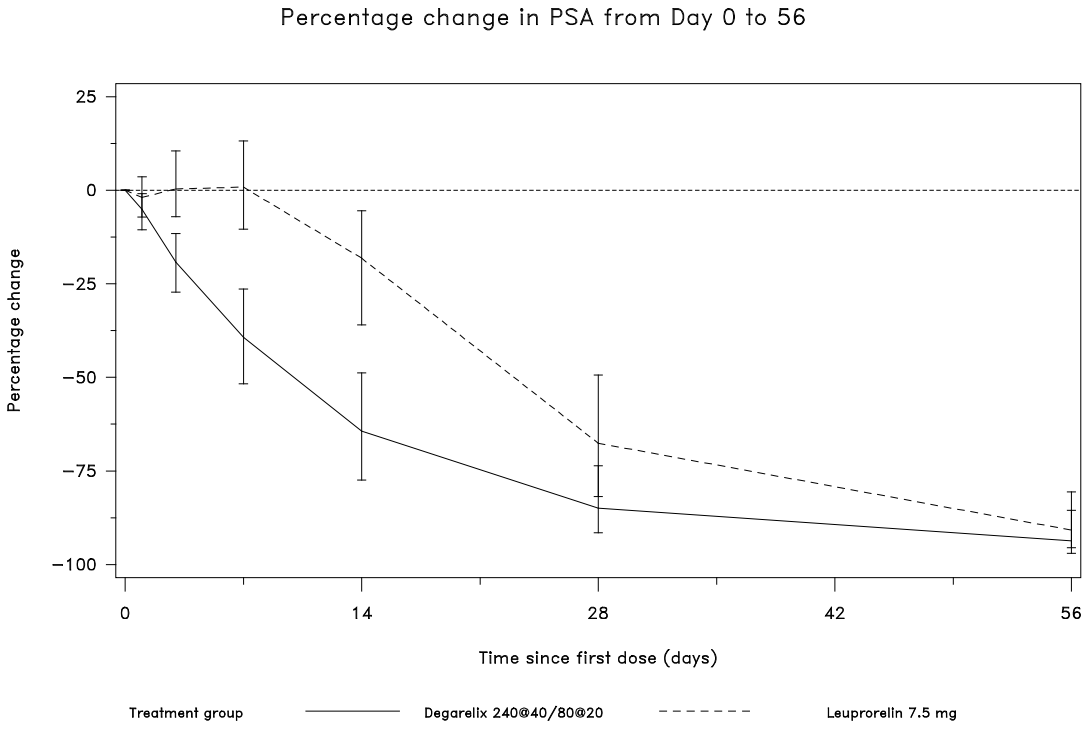
Attainment of prostate specific antigen (PSA) reduction

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
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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with FIRMAGON in all subsets of the paediatric population (see section 4.2 for information on paediatric use).

5.2 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. C_{max} 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.

5.3 Preclinical safety data

Animal reproduction studies showed that degarelix caused infertility in male animals. This is due to the pharmacological effect; and the effect was reversible.

In female reproduction toxicity studies degarelix revealed findings expected from the pharmacological properties. It caused a dosage dependent prolongation of the time to mating and to pregnancy, a reduced number of *corpora lutea*, and an increase in the number of pre- and post-implantation losses, abortions, early embryo/foetal deaths, premature deliveries and in the duration of parturition.

Preclinical studies on safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential revealed no special hazard for humans. Both *in vitro* and *in vivo* studies showed no signs of QT prolongation.

No target organ toxicity was observed from acute, subacute and chronic toxicity studies in rats and monkeys following subcutaneous administration of degarelix. Drug-related local irritation was noted in animals when degarelix was administered subcutaneously in high doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Mannitol (E421)

Solvent
Water for injections

6.2 Incompatibilities

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

6.3 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.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

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

Pre-filled glass (type I) syringes with elastomer plunger stopper, tip cap and line-marking at 3 ml containing 3 ml solvent
Plunger rods
Vial adapters
Injection needles (25G 0.5 x 25 mm)

Pack size
Pack-size of 2 trays containing 2 powder vials, 2 solvent pre-filled syringes, 2 plunger rods, 2 vial adapters and 2 needles

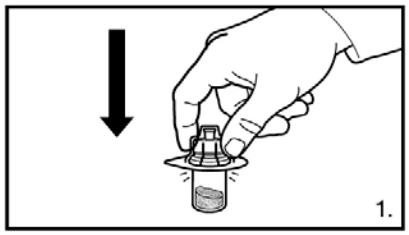
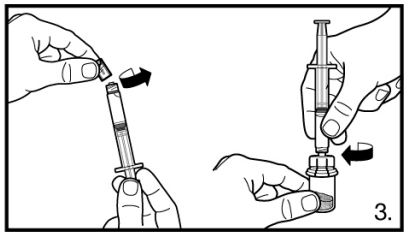
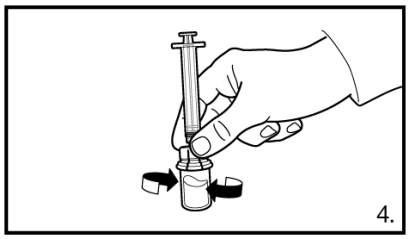
6.6 Special precautions for disposal and other handling

The instructions for reconstitution must be followed carefully.

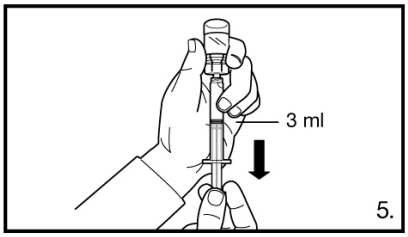
Administration of other concentrations is not recommended because the gel depot formation is influenced by the concentration. The reconstituted solution should be a clear liquid, free of undissolved matter.

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.

<table>
<tr><td> 
</td><td>1. Remove the cover from the vial adapter pack. Attach the adapters to the powder vial by pressing the adapter down until the spike pushes through the rubber stopper and the adapter snaps in place.</td></tr>
<tr><td colspan="2">2. Prepare the pre-filled syringe by attaching the plunger rod.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
<tr><td> 
</td><td>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.

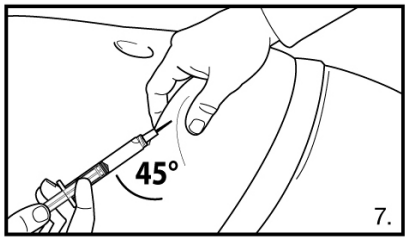
A ring of small air bubbles on the surface of the liquid is acceptable. The reconstitution procedure usually takes a few minutes, but may take up to 15 minutes in some cases.</td></tr>
</table>



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.**

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
DK-2300 Copenhagen S
Denmark
Tel: +45 88 33 88 34

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/504/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17/02/2009
Date of latest renewal: 19/09/2013

10. DATE OF REVISION OF THE TEXT

{DD/MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release
Ferring GmbH
Wittland 11
D-24109 Kiel
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted
- At the request of the European Medicines Agency
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall agree the details of an educational programme with the National Competent Authorities and must implement such programme nationally to ensure that, prior to prescribing, all physicians are provided with a healthcare professional information pack containing the following:
- Educational material
- Summary of Product Characteristics (SPC) and Package Leaflet and Labelling

Key elements to be included in the educational material
- Posology
- Instructions for administration
- Information on gel depot formation and possible injections site reactions
- Information on the identified and potential risks

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR FIRMAGON 80 mg powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

FIRMAGON 80 mg powder and solvent for solution for injection
degarelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 80 mg degarelix (as acetate). After reconstitution each ml of the solution contains 20 mg degarelix.

3. LIST OF EXCIPIENTS

Mannitol (E421), water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack-size of 1 tray containing
1 vial with 80 mg degarelix (powder)
1 pre-filled syringe with 4.2 ml solvent
1 plunger rod
1 vial adapter
1 injection needle

Pack-size of 3 trays containing
3 vials with 80 mg degarelix (powder)
3 pre-filled syringe with 4.2 ml solvent
3 plunger rod
3 vial adapter
3 injection needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 Copenhagen S
Denmark
+45 88 33 88 34

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/504/001 Pack-size of 1 tray
EU/1/08/504/003 Pack-size of 3 trays

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL FOR FIRMAGON 80 mg powder for solution for injection

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

FIRMAGON 80 mg powder for injection
degarelix
SC use only

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE FOR SOLVENT 4.2 ml water for injections

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for FIRMAGON

Water for injections

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4.2 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR FIRMAGON 120 mg powder and solvent for solution for injection

1. NAME OF THE MEDICINAL PRODUCT

FIRMAGON 120 mg powder and solvent for solution for injection
degarelix

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Mannitol (E421), water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Pack-size of 2 trays containing:
2 vials with 120 mg degarelix (powder)
2 pre-filled syringes with 3 ml solvent
2 plunger rods
2 vial adapters
2 injection needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals A/S
Kay Fiskers Plads 11
2300 Copenhagen S
Denmark
+45 88 33 88 34

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/504/002

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL FOR FIRMAGON 120 mg powder for solution for injection

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

FIRMAGON 120 mg powder for injection
degarelix
SC use only

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE FOR SOLVENT 3 ml water for injections

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for FIRMAGON
Water for injections

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

FIRMAGON 80 mg powder and solvent for solution for injection
Degarelix

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any of the side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What FIRMAGON is and what it is used for

FIRMAGON contains degarelix.
Degarelix is a synthetic hormone blocker used in the treatment of prostate cancer in adult male patients. Degarelix mimics a natural hormone (gonadotrophin-relasing hormone, GnRH) and directly blocks its effects. By doing so, degarelix immediately reduces the level of the male hormone testosterone that stimulates the prostate cancer.

2. What you need to know before you use FIRMAGON

Do not use FIRMAGON
- If you are allergic to degarelix or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Please tell your doctor if you have any of the following:
- Any cardiovascular conditions or heart rhythm problems (arrythmia), or are being treated with medicines for this condition. The risk of heart rhythm problems may be increased when using FIRMAGON.
- Diabetes mellitus. Worsening or onset of diabetes may occur. If you have diabetes, you may have to measure blood glucose more frequently.
- Liver disease. Liver function may need to be monitored.
- Kidney disease. Use of FIRMAGON has not been investigated in patients with severe kidney disease.
- Osteoporosis or any condition that affects the strenght of your bones. Reduced level of testosterone may cause a reduction in bone calcium (thinning of bones).
- Severe hypersensitivity. Use of FIRMAGON has not been investigated in patients with severe hypersensitivity reactions.

Children and adolescents
Do not give this medicine to children or adolescents.

Other medicines and FIRMAGON

FIRMAGON might interfere with some medicines used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol) or other medicines which can have an effect on heart rhythm (e.g. methadone (used for pain relief and as part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics).

Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Driving and using machines
Tiredness and dizziness are common side effects that may impair your ability to drive and use machines. These side effects may be due to the treatment or effects resulting from the underlying disease.

3. How to use FIRMAGON

This medicine is usually injected by a nurse or a doctor.

The recommended starting dose is two consecutive injections of 120 mg. After that, you will receive a monthly 80 mg injection. The injected liquid forms a gel from which degarelix is released over a period of one month.

FIRMAGON must be injected under the skin (subcutaneously) ONLY. FIRMAGON must NOT be given into a blood vessel (intravenously). Precautions must be taken to avoid accidental injection into a vein. The site of injection is likely to vary within the abdominal region.

If you forget to use FIRMAGON
If you believe your monthly dose of FIRMAGON has been forgotten, please talk to your doctor.
If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

A very serious allergic reaction to this medicine is rare. Seek medical advice straight away if you develop a severe rash, itching or shortness of breath or difficulty breathing. These could be symptoms of a severe allergic reaction.

Very common (may affect more than 1 in 10 people)
Hot flushes, injection site pain and redness. Side effects at the injection site are most common with the starting dose and less common with the maintenance dose.

Common (may affect up to 1 in 10 people)
- injection site swelling, node and hardness
- chills, fever or influenza-like illness after the injection
- trouble sleeping, tiredness, dizziness, headache
- increased weight, nausea, diarrhoea, elevated levels of some liver enzymes
- excessive sweating (including night sweats), rash
- anaemia
- musculoskeletal pain and discomfort
- reduced size of testicles, breast swelling, impotence

Uncommon (may affect up to 1 in 100 people)
- loss of sexual desire, testicular pain, pelvic pain, ejaculation failure, genital irritation, breast pain
- depression, mental impairment

- skin redness, loss of hair, skin nodule, numbness
- allergic reactions, hives, itching
- decreased appetite, constipation, vomiting, dry mouth, abdominal pain and discomfort, increased blood sugar/diabetes mellitus, increased cholesterol, changes in blood calcium, decreased weight
- high blood pressure, changes in heart rhythm, changes in ECG (QT-prolongation), feeling of abnormal heart beat, dyspnoea, peripheral oedema
- muscular weakness, muscle spasms, joint swelling/stiffness, osteoporosis/osteopenia, pain in the joint
- frequent urination, urinary urgency (must hurry to pass urine), difficult or painful urination, urination at night, impaired renal function, incontinence
- blurred vision
- discomfort at injection including decreased blood pressure and heart rate (vasovagal reaction)
- malaise

Rare (may affect up to 1 in 1,000 people)
- febrile neutropenia (very low number of white blood cell in combination with fever), heart attack, heart failure

Very rare (may affect up to 1 in 10,000 people)
- injection site infection, abscess and necrosis

Reporting of side effects
If you get any of the side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store FIRMAGON

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vials, syringes and outer packaging. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

After reconstitution:
This medicine is stable for 2 hours at 25ºC.
Due to the risk of microbial contamination, this medicine should be used immediately. If not used immediately, the use of this medicine are the responsibility of the user.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What FIRMAGON contains
- The active substance is degarelix, each vial contains 80 mg degarelix (as acetate). After reconstitution 1 ml of the reconstituted solution contains 20 mg degarelix.
- The other ingredient of the powder is mannitol (E 421).
- The solvent is water for injections.

What FIRMAGON looks like and contents of the pack
FIRMAGON is a powder and solvent for solution for injection. The powder is white to off-white. The solvent is a clear, colourless solution.

FIRMAGON is available in 2 pack-sizes.

Pack-size of 1 tray containing:
1 vial with powder containing 80 mg of degarelix and 1 pre-filled syringe with 4.2 ml of solvent.
1 plunger rod, 1 vial adapter and 1 injection needle.

Pack-size of 3 trays containing:
3 vials with powder containing 80 mg of degarelix and 3 pre-filled syringes with 4.2 ml of solvent.
3 plunger rods, 3 vial adapters and 3 injection needles.

Not all pack sizes may be marketed.

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Kay Fiskers Plads 11
DK-2300 Copenhagen S
Denmark
Tel. +45 8833 8834

Manufacturer
Ferring GmbH
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Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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contact2@ferring.com

This leaflet was last revised in {MM/YYYY}.

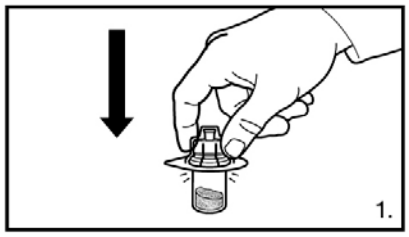
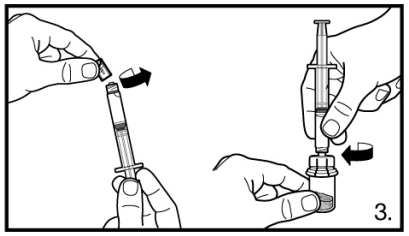
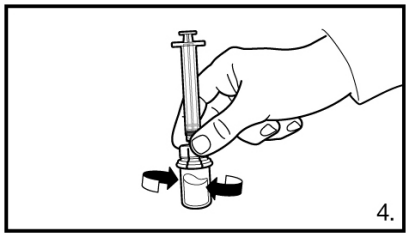
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu/.

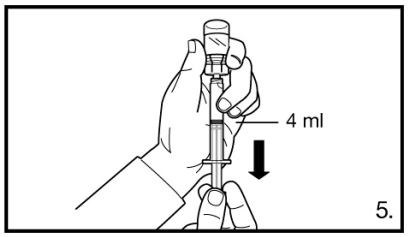
The following information is intended for healthcare professionals only:

Instructions for proper use

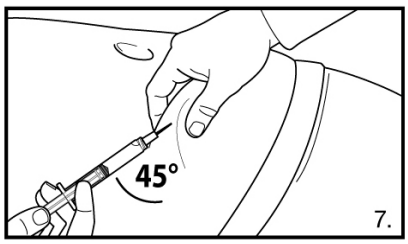
NOTE:
- **DO NOT SHAKE THE VIALS**

The pack contains one vial of powder and one pre-filled syringe with solvent that must be prepared for subcutaneous injection.

<table>
<tr><td> 
</td><td>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.</td></tr>
<tr><td colspan="2">2. Prepare the pre-filled syringe by attaching the plunger rod.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
<tr><td colspan="2">6. Detach the syringe from the vial adapter and attach the needle for deep subcutaneous injection to the syringe.</td></tr>
</table>



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 **4 ml of FIRMAGON 80 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).

* 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.

Package leaflet: Information for the user

FIRMAGON 120 mg powder and solvent for solution for injection
Degarelix

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any of the side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What FIRMAGON is and what it is used for

FIRMAGON contains degarelix.
Degarelix is a synthetic hormone blocker used in the treatment of prostate cancer in adult male patients. Degarelix mimics a natural hormone (gonadotrophin-relasing hormone, GnRH) and directly blocks its effects. By doing so, degarelix immediately reduces the level of the male hormone testosterone that stimulates the prostate cancer.

2. What you need to know before you use FIRMAGON

Do not use FIRMAGON
- If you are allergic to degarelix or any of the other ingredients this medicine (listed in section 6).

Warnings and precautions
Please tell your doctor if you have any of the following:
- Any cardiovascular conditions or heart rhythm problems (arrythmia), or are being treated with medicines for this condition. The risk of heart rhythm problems may be increased when using FIRMAGON.
- Diabetes mellitus. Worsening or onset of diabetes may occur. If you have diabetes, you may have to measure blood glucose more frequently.
- Liver disease. Liver function may need to be monitored.
- Kidney disease. Use of FIRMAGON has not been investigated in patients with severe kidney disease.
- Osteoporosis or any condition that affects the strenght of your bones. Reduced level of testosterone may cause a reduction in bone calcium (thinning of bones). Severe hypersensitivity. Use of FIRMAGON has not been investigated in patients with severe hypersensitivity reactions.

Children and adolescents
Do not give this medicine to children or adolescents.

Other medicines and FIRMAGON
FIRMAGON might interfere with some medicines used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol) or other medicines which can have an effect on heart rhythm (e.g.

methadone (used for pain relief and part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics).

Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Driving and using machines
Tiredness and dizziness are common side effects that may impair your ability to drive and use machines. These side effects may be due to the treatment or effects resulting from the underlying disease.

3. How to use FIRMAGON

This medicine is usually injected by a nurse or a doctor.

The recommended starting dose is two consecutive injections of 120 mg After that, you will receive a monthly 80 mg injection. The injected liquid forms a gel from which degarelix is released over a period of one month.

FIRMAGON must be injected under the skin (subcutaneously) ONLY. FIRMAGON must NOT be given into a blood vessel (intravenously). Precautions must be taken to avoid accidental injection into a vein. The site of injection is likely to vary within the abdominal region.

If you forget to use FIRMAGON
If you believe your monthly dose of FIRMAGON has been forgotten, please talk to your doctor.
If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

A very serious allergic reaction to this medicine is rare. Seek medical advice straight away if you develop a severe rash, itching or shortness of breath or difficulty breathing. These could be symptoms of a severe allergic reaction.

Very common (may affect more than 1 in 10 people)
Hot flushes, injection site pain and redness. Side effects at the injection site are most common with the starting dose and less common with the maintenance dose.

Common (may affect up to 1 in 10 people)
- injection site swelling, node and hardness
- chills, fever or influenza-like illness after the injection
- trouble sleeping, tiredness, dizziness, headache
- increased weight, nausea, diarrhoea, elevated levels of some liver enzymes
- excessive sweating (including night sweats), rash
- anaemia
- musculoskeletal pain and discomfort
- reduced size of testicles, breast swelling, impotence

Uncommon (may affect up to 1 in 100 people)
- loss of sexual desire, testicular pain, pelvic pain, ejaculation failure, genital irritation, breast pain
- depression, mental impairment
- skin redness, loss of hair, skin nodule, numbness
- allergic reactions, hives, itching

- decreased appetite, constipation, vomiting, dry mouth, abdominal pain and discomfort, increased blood sugar/diabetes mellitus, increased cholesterol, changes in blood calcium, decreased weight
- high blood pressure, changes in heart rhythm, changes in ECG (QT-prolongation), feeling of abnormal heart beat, dyspnoea, peripheral oedema
- muscular weakness, muscle spasms, joint swelling/stiffness, osteoporosis/osteopenia, pain in the joint
- frequent urination, urinary urgency (must hurry to pass urine), difficult or painful urination, urination at night, impaired renal function, incontinence
- blurred vision
- discomfort at injection including decreased blood pressure and heart rate (vasovagal reaction)
- malaise

Rare (may affect up to 1 in 1,000 people)
- febrile neutropenia (very low number of white blood cell in combination with fever), heart attack, heart failure

Very rare (may affect up to 1 in 10,000 people)
- injection site infection, abscess and necrosis

Reporting of side effects
If you get any of the side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store FIRMAGON

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vials, syringes and outer packaging. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

After reconstitution
This medicine is stable for 2 hours at 25ºC.
Due to the risk of microbial contamination, this medicine should be used immediately. If not used immediately, the use of this medicine are the responsibility of the user.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What FIRMAGON contains

- The active substance is degarelix. Each vial contains 120 mg degarelix (as acetate). After reconstitution 1 ml of the reconstituted solution contains 40 mg degarelix.
- The other ingredient of the powder is mannitol (E 421).
- The solvent is water for injections.

What FIRMAGON looks like and contents of the pack

FIRMAGON is a powder and solvent for solution for injection. The powder is white to off-white. The solvent is a clear, colourless solution.

Pack-size of 2 trays containing:
2 vials with powder containing 120 mg of degarelix and 2 pre-filled syringes with 3 ml of solvent.
2 plunger rods, 2 vial adapters and 2 injection needles.

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This leaflet was last revised in {MM/YYYY}.

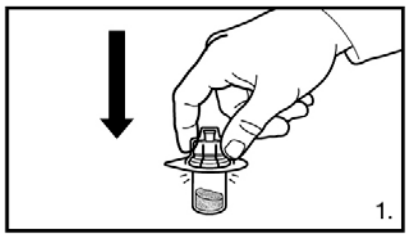
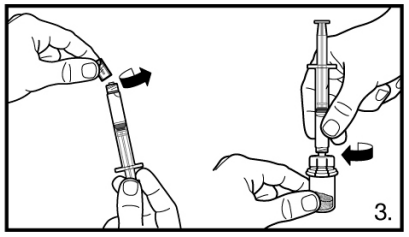
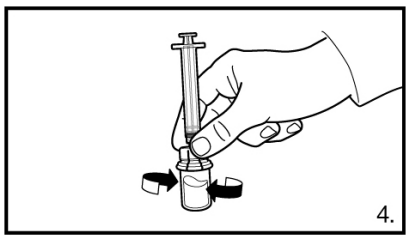
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

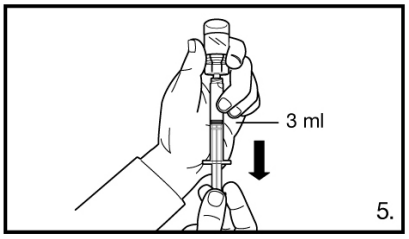
The following information is intended for healthcare professionals only:

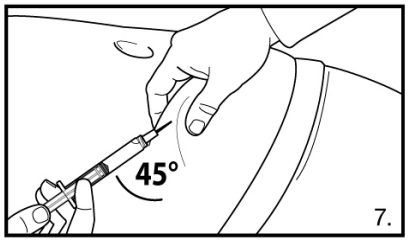
Instructions for proper use

NOTE:
- **DO NOT SHAKE THE VIALS**

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.

<table>
<tr><td> 
</td><td>1. Remove the cover from the vial adapter pack. Attach the adapters to the powder vial by pressing the adapter down until the spike pushes through the rubber stopper and the adapter snaps in place.</td></tr>
<tr><td colspan="2">2. Prepare the pre-filled syringe by attaching the plunger rod.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
<tr><td> 
</td><td>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.</td></tr>
<tr><td> 
</td><td>5. Turn the vial upside down and draw up to the line mark of the syringe for injection.

Always make sure to withdraw the precise volume and adjust for any air bubbles.</td></tr>
<tr><td colspan="2">6. Detach the syringe from the vial adapter and attach the needle for deep subcutaneous injection to the syringe.</td></tr>
<tr><td> 
</td><td>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.*</td></tr>
</table>

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.