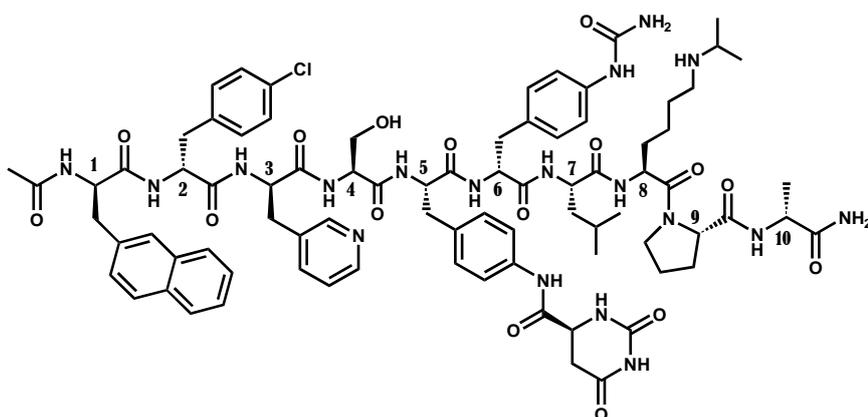


FIRMAGON[®] degarelix (as acetate)
FIRMAGON 120 mg, powder and solvent for injection, depot
FIRMAGON 80 mg, powder and solvent for injection, depot

NAME OF THE MEDICINE

Degarelix (as acetate). Degarelix is a third generation gonadotrophin releasing hormone (GnRH) antagonist (blocker). It is a synthetic decapeptide, which forms a depot following subcutaneous injection; this depot formation results in a sustained release of degarelix.

The structural formula of degarelix is



It has an empirical formula of $C_{82}H_{103}N_{18}O_{16}Cl$ and a monoisotopic mass of 1630.75 Da. CAS Number: 214766-78-6.

DESCRIPTION

FIRMAGON is a sterile, off-white powder plus a clear, colourless solvent for reconstitution. The sterile powder is a freeze-dried product containing degarelix (as the acetate) and mannitol. The solvent consists of sterile water for injections. FIRMAGON delivers degarelix acetate, equivalent to 120 mg of degarelix for the starting dose, and 80 mg of degarelix for the maintenance dose. The 80 mg vial contains 200 mg mannitol and the 120 mg vial contains 150 mg mannitol.

Degarelix has a natural propensity to gel in aqueous media by its inherent physicochemical characteristics. At concentrations above ca. 1 mg/mL, aqueous degarelix aggregates and cross-links in a gel-forming network, resulting in the formation of a hydrogel. While the process does not take place visibly in the reconstituted product, the depot formation happens instantaneously following subcutaneous administration.

PHARMACOLOGY

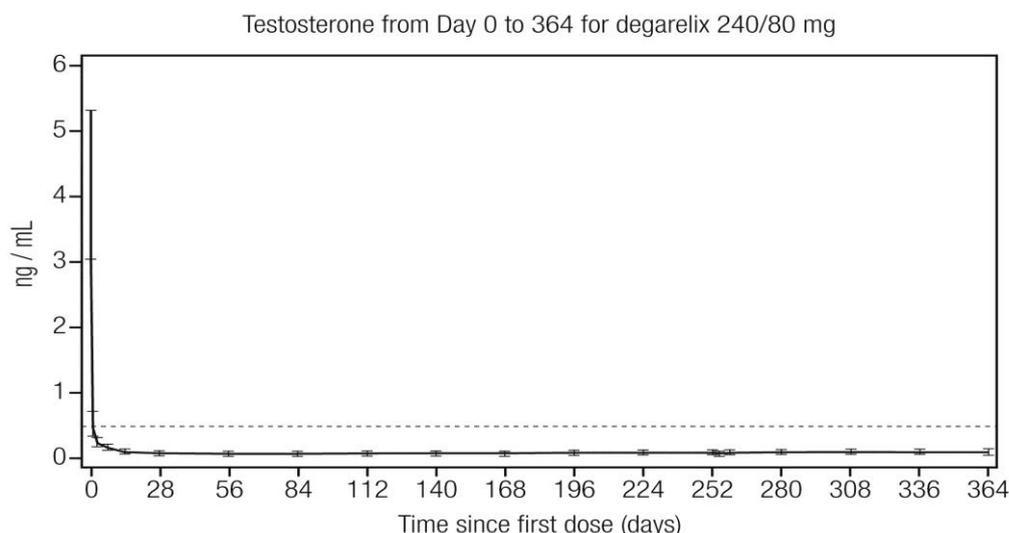
Pharmacodynamics

Degarelix is a selective GnRH receptor antagonist (blocker) that competitively and reversibly binds to the pituitary GnRH receptors with nanomolar potency, thereby rapidly reducing the release of gonadotrophins and consequently testosterone (T). Prostate cancer is sensitive to testosterone deprivation, a mainstay principle in the treatment of hormone-sensitive prostate cancer. Unlike GnRH agonists, GnRH receptor blockers do not induce a luteinising hormone (LH) surge with subsequent testosterone surge/tumour stimulation and potential symptomatic flare after the initiation of treatment.

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

FIRMAGON 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. Median testosterone levels after one year of treatment were 0.087 ng/mL [interquartile range 0.06-0.15] N=167.

Figure 1: Plasma testosterone levels from day 0 to 364 for degarelix 240 mg/80 mg (median with interquartile ranges).



Pharmacokinetics

Absorption

FIRMAGON forms a depot upon subcutaneous administration, from which degarelix is released to the circulation. The relevant pharmacokinetic results of FIRMAGON evaluated in prostate cancer patients are summarised in Table 1. Median degarelix trough concentrations in the maintenance phase with 80 mg at a concentration of 20 ng/mL was 10.9 ng/mL.

Table 1: Pharmacokinetic parameters after subcutaneous administration of FIRMAGON 240 mg at a concentration of 40 mg/mL (single dose). Median (5-95 percentiles), *observed values day 0-28, **model estimated values.

Pharmacokinetic parameter	FIRMAGON 240 mg
C _{max} (ng/mL)*	53.4 (27.3-126.5)
T _{max} (days)**	1.4 (1.1-2.0)
T _{1/2} (days)**	43 (27-73)
AUC _{0-∞} (day·ng/mL)**	1240 (733-2140)

Following subcutaneous administration of 240 mg FIRMAGON at a concentration of 40 mg/mL to prostate cancer patients, degarelix reaches a maximal concentration after 1-2 days and decreases thereafter in a biphasic fashion, with a median terminal half-life of approximately 43 days. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the FIRMAGON depot formed at the injection site(s). The pharmacokinetic behaviour of the drug is influenced by its concentration in the injection. The estimated values for bioavailability from population pharmacokinetic modelling were approximately 60% and 40% for dose concentrations 20 mg/mL and 40 mg/mL respectively.

Distribution

The distribution volume at steady state in healthy elderly men (≥65 years) was in the range of 0.65-0.82 L/kg. Plasma protein binding is estimated to be approximately 90%.

Metabolism

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.

Excretion

In healthy men, approximately 20-30% of a given dose of degarelix was renally excreted, suggesting that approximately 70-80% is excreted via the hepato-biliary system in humans. The clearance in healthy elderly men is 35-50 mL/h/kg. After i.v. administration terminal half-life was 10-16 hours which is much shorter than for s.c. administration, indicating that the observed terminal phase after s.c. administration is determined by the absorption rate rather than the elimination rate.

CLINICAL TRIALS

The efficacy and safety of FIRMAGON was evaluated in an open-label, multi-centre, randomised, active comparator, parallel-group study. The study investigated the efficacy and safety of FIRMAGON one month dosing regimens; a starting dose of 240 mg (40 mg/mL) followed by monthly doses of 160 mg (40 mg/mL) or 80 mg (20 mg/mL) s.c., in comparison to leuprorelin 7.5 mg i.m. in patients with prostate cancer requiring androgen deprivation therapy. In total 620 patients were randomised to one of the three treatment groups.

Of the patients randomised

- 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 primary objective was to demonstrate that FIRMAGON is effective with respect to achieving and maintaining testosterone suppression to below 0.5 ng/mL, during 12 months treatment. In total 504 (81%) patients completed the study. In the degarelix treatment group 240/80 mg, 41 (20%) patients and in the leuprorelin treatment group, 32 (16%) patients discontinued the study.

The primary efficacy endpoint of the study was the cumulative probability of testosterone \leq 0.5 ng/mL from Day 28 through Day 364.

For each of the three treatment groups, the cumulative one-year testosterone suppression probabilities were estimated using the Kaplan Meier method applied to time to testosterone $>$ 0.5 ng/mL from Day 28 to Day 364. Associated 95% confidence intervals (CI) were calculated using the log-log transformation of survivor function, Greenwood's formula and the delta-method. Differences in one-year testosterone suppression rates between the degarelix treatment groups and leuprorelin 7.5 mg were assessed using a 97.5% CI (i.e. multiplicity adjusted) calculated by normal approximation using the pooled standard error.

To assess the efficacy of degarelix, two hypotheses were tested:

One criterion was to determine whether the one-year cumulative suppression rate was statistically significantly larger than 90%, that is, whether the lower bound of the 95% confidence interval (CI) for the cumulative probability of testosterone \leq 0.5 ng/mL from Day 28 to Day 364 was not lower than 90%. The second criterion was to determine whether degarelix was non-inferior to leuprorelin 7.5 mg with respect to the cumulative probability of testosterone \leq 0.5 ng/mL from Day 28 to Day 364. The non-inferiority limit for the difference between treatments (degarelix versus leuprorelin 7.5 mg) was -10 percentage points.

The trial was powered, assuming true cumulative suppression rates of 96% and 15 % annual drop out rate, for each treatment arm, to meet, with >90% probability (power), each of the efficacy criteria. Power calculations were based on simulation experiments and the above mentioned analysis methods.

The results are presented in Tables 2-a and 2-b and in Figure 2.

Table 2-a: Primary endpoint (first criterion): Kaplan-Meier estimates of the cumulative probability of testosterone ≤ 0.5 ng/mL from day 28 to day 364 – ITT analysis set

	Degarelix 240/160 mg (N=202)			FIRMAGON 240/80 mg (N=207)			Leuprorelin 7.5 mg (N=201)		
	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)
Day 28 → 364	3	199	(98.3%)	5	202	(97.2%)	7	194	(96.4%)
95% CI			[94.8;99.4%]			[93.5;98.8%]			[92.5;98.2%]

T>0.5 ng/mL = Cumulative number of patients with testosterone >0.5 ng/mL

Cens = Number of censored observations before or at Day 364

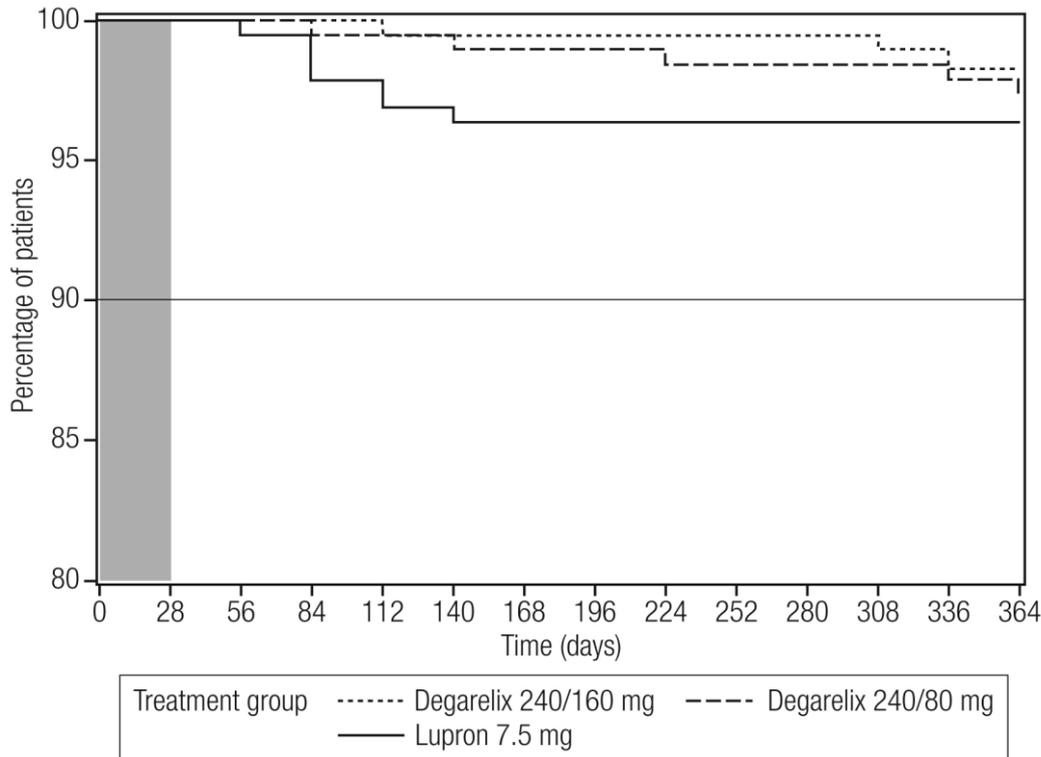
(%) = Estimated probability of all testosterone values ≤ 0.5 ng/mL

Table 2-b: Primary endpoint (second criterion): Difference in Kaplan-Meier estimates of the cumulative probability of testosterone ≤ 0.5 ng/mL from day 28 to day 364 between degarelix and leuprorelin arms – ITT analysis set

Degarelix 240/160 mg (N=202)		FIRMAGON 240/80 mg (N=207)	
Estimate (%)	97.5% CI (%)	Estimate (%)	97.5% CI (%)
1.9%	[-1.8;5.7%]	0.9%	[-3.2;5.0%]

Note: the non-inferiority margin for the difference to leuprorelin 7.5 mg is -10 percentage points, the Lower Limit of the 97.5% CI is to be larger than -10 percent points to claim non-inferiority to leuprorelin

Figure 2: Kaplan-Meier plot of the cumulative probability of testosterone ≤ 0.5 ng/mL from day 28 and onwards – ITT analysis set



Tables 2-a and 2-b indicate that the primary endpoint according to both criteria has been met. Both degarelix arms have statistically significantly demonstrated a response larger than 90% and have proven to be non-inferior to leuprorelin. Figure 2 depicts, by means of a Kaplan-Meier plot, the cumulative probability of T ≤ 0.5 ng/mL as a function of time for each treatment arm.

Similar results were obtained for the per-protocol analysis set.

In addition the study included a range of secondary endpoints relating to testosterone suppression and PSA levels.

Attainment of serum Testosterone (T) ≤ 0.5 ng/mL:

FIRMAGON is effective in achieving fast testosterone suppression, see Table 3

Table 3: Percentage of patients attaining T ≤ 0.5 ng/mL after start of treatment

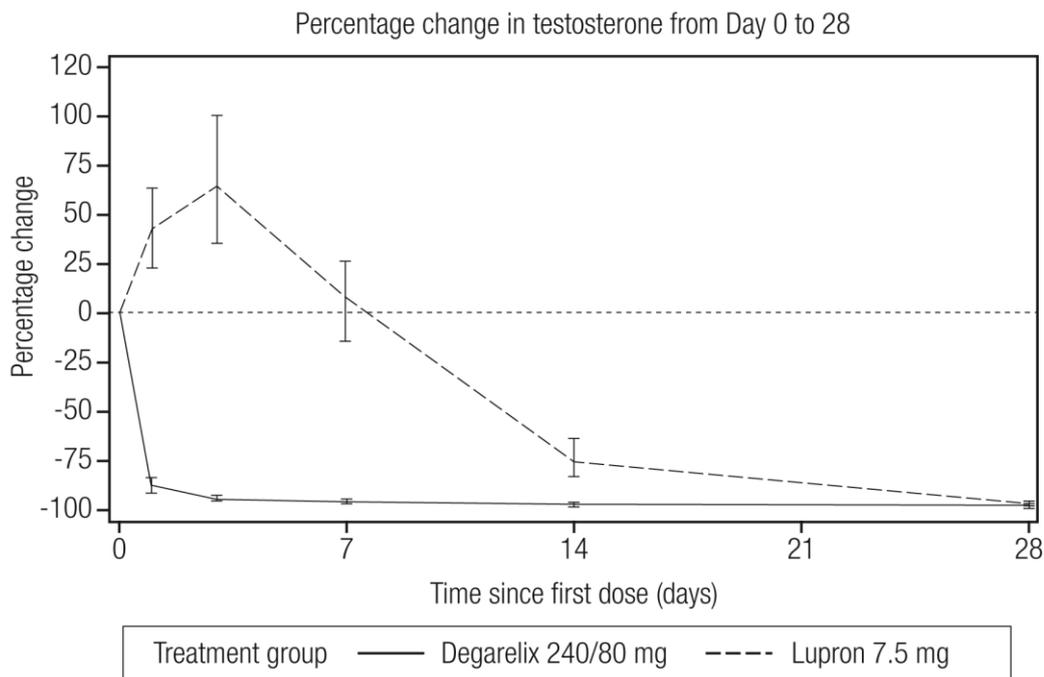
Time	FIRMAGON 240/80 mg s.c.	Leuprorelin 7.5 mg i.m.
Day 1	52%	0%
Day 3	96%	0%
Day 7	99%	1%
Day 14	100%	18%
Day 28	100%	100%

Avoidance of testosterone surge:

None of the FIRMAGON 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. Surge was defined as testosterone exceeding baseline by $\geq 15\%$ within the first 2 weeks. This difference was statistically significant ($p < 0.001$).

Serum levels of testosterone over time:

Figure 3: Percentage change in testosterone from baseline by treatment group until day 28 (median with interquartile ranges)



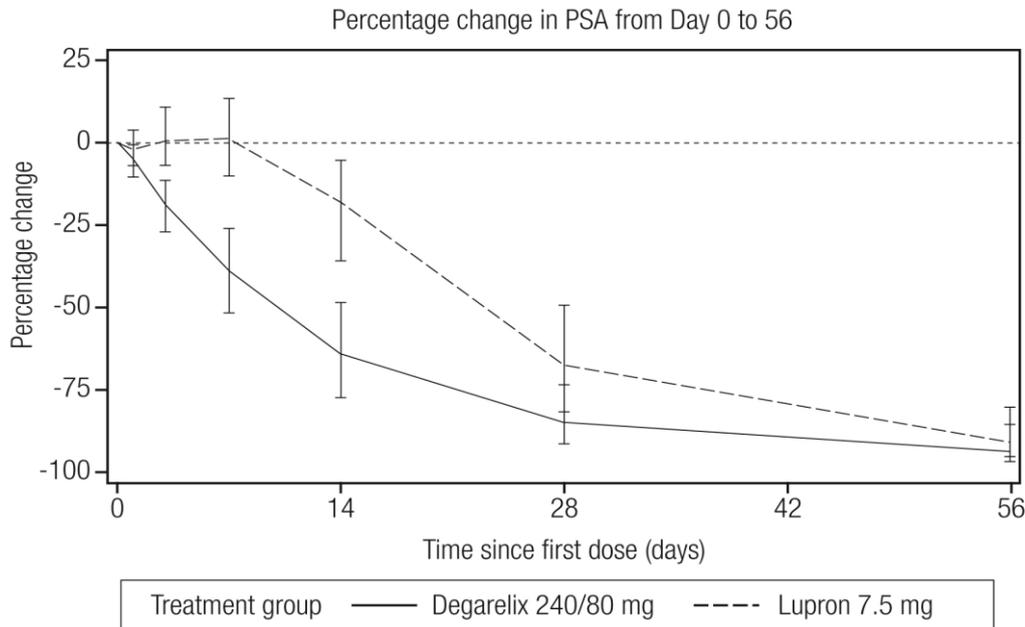
Attainment of prostate specific antigen (PSA) reduction:

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 FIRMAGON.

The median PSA in the study at baseline was:

- for the FIRMAGON 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 4: Percentage change in PSA from baseline by treatment group until day 56 (median with interquartile ranges)



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

Prostate specific antigen (PSA) levels are lowered by 64% two weeks after administration of FIRMAGON, 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 FIRMAGON and the comparator in the percentage change from baseline.

Change in ECGs:

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 12.3 msec (3.2%) and for leuprorelin was 16.7 msec (3.5%).

Anti-degarelix antibody development has been observed in 10% of patients after treatment with FIRMAGON for 1 year. There is no indication that the efficacy or safety of FIRMAGON treatment is affected by antibody formation.

INDICATIONS

FIRMAGON is a GnRH receptor blocker indicated for treatment of patients with prostate cancer in whom androgen deprivation is warranted.

CONTRAINDICATIONS

Hypersensitivity to degarelix or any other GnRH antagonists, or to any of the product excipients. FIRMAGON is not indicated in women or paediatric patients.

PRECAUTIONS

Effect on QT/QTc interval

Long-term androgen deprivation therapy may prolong the QT interval (See PHARMACOLOGY). In the confirmatory study comparing FIRMAGON to leuprorelin periodic (monthly) ECGs were performed; changes in ECG measurements seen during one year of treatment were in the same range for degarelix and a GnRH-agonist (leuprorelin) used as comparator. Both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients. 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 \geq 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.

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 (e.g. Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications). Therefore in such patients, the benefit/risk ratio of FIRMAGON must be thoroughly appraised. A thorough QT study in healthy men showed that there was no intrinsic effect of degarelix on QT/QTc interval.

Hypersensitivity

Patients in the degarelix program were carefully monitored post-injection for at least one hour at all dosing visits in order to detect any untoward effects that may be histamine mediated. Consequently, more than 1,700 patients at more than 19,000 dosing occasions have been observed. No cases of anaphylaxis, angioedema, or severe cutaneous skin reactions related to degarelix treatment have been observed.

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.

Antibody formation

Anti-degarelix antibody development has been observed in 10% of patients after treatment with FIRMAGON for one year. The prevalence of anti-degarelix antibodies increased with time. There is no indication that the efficacy or safety of FIRMAGON treatment is affected by antibody formation.

Changes in hepatic enzyme measurements

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. Changes in laboratory values seen during one year of treatment were in the same range for degarelix and the 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.

Route of administration

FIRMAGON is for subcutaneous administration only and is not to be administered intravenously.

Second line use

There are no data available on use of FIRMAGON in patients in whom treatment with GnRH agonists (e.g. leuprorelin, goserelin) has failed. FIRMAGON should only be used as first line androgen deprivation therapy.

Effects on fertility

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

Use in Pregnancy (Category D)

FIRMAGON must not be used in pregnant women (see CONTRAINDICATIONS). Potential embryofetal effects were assessed with subcutaneous doses of degarelix during the period of organogenesis in rats at up to 0.09 mg/kg/day and in rabbits at up to 0.006 mg/kg/day, approximately 10% and 2% of the clinical dose on a mg/m² basis. An increase in the number of abortions, early embryofetal deaths and premature deliveries along with prolonged parturition were observed in both studies.

Genotoxicity

Degarelix did not cause genetic damage in standard *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration) nor in *in vivo* rodent bone marrow micronucleus tests.

Carcinogenicity

Two rodent carcinogenicity studies were performed with degarelix using maximum s.c doses of 50 mg/kg/2 weeks in mice and 25 mg/kg/2 weeks in rats, resulting in at least 7-fold the clinical AUC. No neoplastic changes were observed in male animals in either of these studies. An increase in hepatocellular adenomas was observed in female mice at all doses of degarelix tested, most likely as a result of reduced oestrogen. The incidence of haemangiosarcoma in the mesenteric lymph node of the female rats was increased at 25 mg/kg/2 weeks.

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 3 study has demonstrated that the clearance of degarelix in patients with moderate renal impairment is reduced by 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 category.

Patients with hepatic impairment

Degarelix has been studied in a pharmacokinetic study in patients with mild to moderate hepatic impairment. No signs of increased exposure in the hepatically impaired were observed compared to healthy subjects. No shifts in liver function tests were observed 24 hours post-dose compared to baseline in patients with hepatic impairment. 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.

Elderly

The patient population tested in the clinical program was typical of the intended target population of patients with prostate cancer. The mean age was 74 years (range 47 to 98 years). Population pharmacokinetic analysis shows only small changes in the clearance of degarelix related to age and weight. Therefore, dose adjustment is not warranted.

Effects on ability to drive and use machines

No studies on the effects of FIRMAGON on the ability to drive and use machines have been performed.

INTERACTION WITH OTHER MEDICINES

No drug-drug interaction studies have been performed.

Degarelix is not a substrate for the human CYP450 system and has been shown not to induce or inhibit CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 to any great extent *in vitro*. Further, degarelix is not a substrate for p-glycoprotein or other human efflux/uptake transporters and is unlikely to interact with other medicines handled by transporters at clinically relevant concentrations. Therefore, clinically significant pharmacokinetic drug-drug interactions are unlikely.

ADVERSE EFFECTS

The most commonly observed adverse reactions during FIRMAGON therapy in the confirmatory Phase 3 study 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) and injection site adverse events.

The injection site adverse events reported were mainly pain and erythema, reported in 28% and 17% of patients, respectively, less frequently reported were swelling (6%), induration (4%) and nodule (3%). These events occurred primarily with the starting dose whereas during maintenance therapy the incidence of these events per 100 injections were: 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, such as injection site infection, injection site abscess or injection site necrosis that could require surgical treatment/drainage, were reported rarely.

The following adverse events were reported in 5% or more of patients in an active controlled trial comparing treatment with degarelix and leuprorelin, given as monthly administrations for 12 months, in patients with prostate cancer.

	FIRMAPAGON 240/80 mg (s.c.) N = 207	Leuprorelin 7.5 mg (i.m.) N = 201
	%	%
Percentage of subjects with adverse events	79	78
Body as a whole		
Injection site adverse events	35	<1
Weight increase	9	12
Fatigue	3	6
Chills	5	0
Cardiovascular system		
Hot flush	26	21
Hypertension	6	4
Musculoskeletal system		
Back pain	6	8
Arthralgia	5	9
Urogenital system		
Urinary tract infection	5	9
Digestive system		
Increases in transaminases and GGT	10	5
Constipation	5	5

The following adverse events were considered related to degarelix treatment by the investigator in the active controlled trial:

MeDRA System Organ Class (SOC)	Very common (≥ 1/10)	Common (≥ 1/100 and < 1/10)	Uncommon (≥ 1/1000 and < 1/100)
Blood and the lymphatic system disorders			Haemoglobin decreased
Immune system disorders			Hypersensitivity
Psychiatric disorders		Insomnia	Loss of libido
Nervous system disorders		Dizziness, headache	
Vascular disorders	Hot flush*		Hypertension
Gastrointestinal disorders		Nausea, constipation	Diarrhoea
Hepato-biliary disorders		Liver transaminases increased	
Skin and subcutaneous disorders		Night sweats	Urticaria, hyperhidrosis, skin hyperpigmentation

Reproductive system and breast disorders			Erectile dysfunction, testicular atrophy, gynaecomastia
General disorders and administration site conditions	Injection site reaction	Chills, pyrexia, asthenia, fatigue	Influenza-like illness
Investigations		Weight increase*	

*Physiological consequence of testosterone suppression

Erectile dysfunction and loss of libido are common adverse events associated with androgen deprivation therapy.

Post marketing experience

Hypersensitivity reactions, including anaphylaxis, urticaria and angioedema, have been reported rarely in the post-marketing setting with FIRMAGON.

Changes in laboratory parameters

Changes in laboratory values seen during one year of treatment 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, haematocrit (≤ 0.37) and haemoglobin (≤ 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 μ mol/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.

DOSAGE AND ADMINISTRATION

Dosage for Adult Males

Starting dose	Maintenance dose – monthly administration
240 mg administered as two s.c. injections of 120 mg at a concentration of 40 mg/mL	80 mg administered as one s.c. injection at a concentration of 20 mg/mL

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

The therapeutic effect of FIRMAGON should be monitored by clinical parameters and by measuring 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 plasma testosterone at medical castration levels ($T \leq 0.5$ 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 ($T \leq 0.5$ 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 FIRMAGON does not induce a testosterone surge it is not necessary to add an anti-androgen as surge protection at initiation of therapy.

Administration

FIRMAGON is for subcutaneous administration only. IT MUST NOT BE ADMINISTERED INTRAVENOUSLY. Use in one patient on one occasion only. Contains no antimicrobial preservative.

FIRMAGON must be administered immediately after reconstitution. It is administered as a subcutaneous injection in the abdominal region. As with other drugs administered by subcutaneous injection, 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. The injection site should not be rubbed or massaged as this might disperse the depot resulting in altered release.

Reconstitution

FIRMAGON is supplied as a powder to be reconstituted with water for injections (supplied in a pre-filled syringe specific for each presentation). The reconstitution procedure needs to be carefully followed (see below and package insert). Administration of other concentrations is not recommended. The reconstituted product should be a clear liquid, free of undissolved matter.

Reconstitution of FIRMAGON single dose vials:

Presentation	Sterile Water for Injections	Total Product and Volume	Extractable Product and Volume	Final Concentration
120 mg	Add 3 mL	128 mg in 3.2 mL	120 mg in 3 mL	40 mg/mL
80 mg	Add 4.2 mL	88.2 mg in 4.4 mL	80 mg in 4 mL	20 mg/mL

1. Transfer the entire contents of one pre-filled solvent syringe into one powder vial.
2. Hold the vial (with the syringe in place) by the neck and swirl it gently until the liquid looks clear and there is no powder or particulate matter visible. If the powder adheres to the side of the vial above the liquid surface, slightly tilt the vial to dissolve the powder. AVOID SHAKING THE VIAL, in order to prevent foam forming. A ring of small air bubbles on the surface of the liquid is acceptable. This process usually takes a few minutes, but may take up to 15 minutes.
3. Turn the vial upside down and draw up to the line mark on the syringe.
4. Attach the safety needle. Remove any air bubbles.
5. Grasp the skin of the abdomen, pinch the subcutaneous tissue. Prepare to perform a deep subcutaneous injection. To do so, insert the needle **deeply** at an angle of not less than **45 degrees**. DO NOT INJECT DIRECTLY INTO A VEIN. Before injecting, gently pull back the plunger to check if blood is aspirated. If blood appears in the syringe, the reconstituted product can no longer be used. Discontinue the procedure and discard the syringe and needle (reconstitute a new dose for the patient).
6. Inject the dose slowly, immediately after reconstitution.
7. For the 240 mg starter dose, repeat the reconstitution procedure for the second 120 mg dose.

Dose Adjustment in Specific Patient Populations

Elderly, Hepatically or Renally impaired:

There is no need to adjust the dose for the elderly or in patients with mild or moderate liver or kidney function impairment (see PHARMACOLOGY – Pharmacokinetics). Patients with severe liver or kidney dysfunction have not been studied and caution is therefore warranted.

There is no relevant indication for FIRMAGON in women and children.

Incompatibilities

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

OVERDOSAGE

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

PRESENTATION AND STORAGE CONDITIONS

The following pack sizes are available:

Starter dose (120 mg x 2, 40 mg/mL after reconstitution) – 1 procedure pack contains:

2 vials each containing 120 mg powder for injection
2 pre-filled syringes each with line markings at 3 mL containing 3 mL solvent (Water for Injections)
2 plunger rods
2 vial adapters
2 safety needles (25G 0.5 x 25 mm)

Maintenance dose (80 mg, 20 mg/mL after reconstitution) – 1 procedure pack contains:

1 vial containing 80 mg powder for injection
1 pre-filled syringe with line marking at 4 mL containing 4.2 mL solvent (Water for Injections)
1 plunger rod
1 vial adapter
1 safety needle (25G 0.5 x 25 mm)

List of excipients

Powder: Mannitol

Solvent: Water for Injections

Special precautions for storage

Store below 25°C.

Chemical and physical in-use stability of the reconstituted product has been demonstrated for 2 hours at 25°C after solvent addition. From a microbiological point of view, once reconstituted, the product should be administered immediately.

Special precautions for disposal

No special requirements for disposal.

NAME AND ADDRESS OF SPONSOR

Ferring Pharmaceuticals Pty Ltd
Suite 2, Level 1, Building 1
20 Bridge Street
Pymble NSW 2073
Australia

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (S4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

16 February 2010

DATE OF MOST RECENT AMENDMENT

8 September 2015