FIRMAGON® (degarelix for injection)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FIRMAGON® (degarelix for injection) safely and effectively. See full prescribing information for FIRMAGON.

FIRMAGON® (degarelix for injection) for subcutaneous administration
Initial U.S. Approval: 2008

----------RECENT MAJOR CHANGES----------
Warnings and Precautions, Effect on QT/QTc Interval (5.3) 02/2015

----------INDICATIONS AND USAGE----------
FIRMAGON is a GnRH receptor antagonist indicated for treatment of patients with advanced prostate cancer. (1)

----------DOSAGE AND ADMINISTRATION----------
- FIRMAGON is for subcutaneous administration only
- Treatment is started with a dose of 240 mg given as two injections of 120 mg each (2.1)
- The starting dose is followed by maintenance doses of 80 mg administered as a single injection every 28 days (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
- FIRMAGON (degarelix for injection) 120 mg per vial
- FIRMAGON (degarelix for injection) 80 mg per vial

----------CONTRAINDICATIONS----------
FIRMAGON is contraindicated in:
- Patients with previous hypersensitivity reactions to degarelix (4)
- Pregnancy Category X. Fetal harm can occur when administered to pregnant women (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity: Anaphylaxis, urticaria and angioedema have been reported. Discontinue Firmagon if a serious hypersensitivity reaction occurs, and manage as clinically indicated (5.2)
- Effect on QT/QTc Interval: Androgen deprivation therapy may prolong the QT interval. Consider risks and benefits (5.3)

----------ADVERSE REACTIONS----------
The most commonly observed adverse reactions (≥10%) during FIRMAGON therapy included injection site reactions (e.g., pain, erythema, swelling or induration), hot flashes, increased weight, and increases in serum levels of transaminases and gamma-glutamyltransferase (GGT) (6)

To report SUSPECTED ADVERSE REACTIONS, contact Ferring at 1-888-FERRING (1-888-337-7464) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
Clinically significant CYP450 pharmacokinetic drug-drug interactions are unlikely (7)

----------USE IN SPECIFIC POPULATIONS----------
There is no need to adjust the dose for the elderly or in patients with mild or moderate liver or kidney function impairment. Patients with severe liver or kidney dysfunction have not been studied and caution is therefore warranted (8)

See 17 for PATIENT COUNSELING INFORMATION and FDA approved Patient Labeling.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FIRMAGON is a GnRH receptor antagonist indicated for treatment of patients with advanced prostate cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing information

FIRMAGON is administered as a subcutaneous injection in the abdominal region only.

Starting dose	**Maintenance dose – Administration every 28 days**
240 mg given as two subcutaneous injections of 120 mg at a concentration of 40 mg/mL	80 mg given as one subcutaneous injection at a concentration of 20 mg/mL

The first maintenance dose should be given 28 days after the starting dose.

2.2 Reconstitution and Administration Instructions

FIRMAGON® is to be administered by a healthcare professional only. Before administering FIRMAGON read the Instructions for reconstitution and administration carefully.

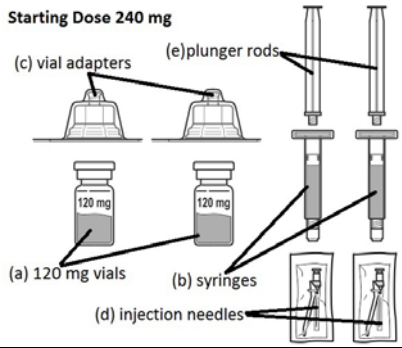
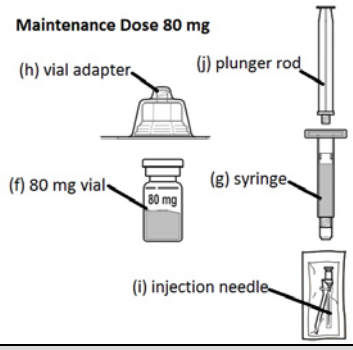
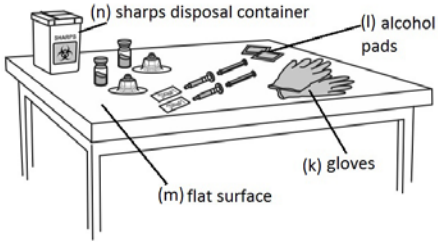
As with other drugs administered by subcutaneous injection, the injection site should vary periodically. Injections should be given in areas of the abdomen that will not be exposed to pressure, e.g., not close to waistband or belt nor close to the ribs.

FIRMAGON is supplied as a powder to be reconstituted with Sterile Water for Injection, USP (WFI).
The instruction for reconstitution needs to be carefully followed. Administration of other concentrations is not recommended. Read the complete instructions before performing the injection.

NOTE: FIRMAGON is for subcutaneous administration to the abdominal region only.

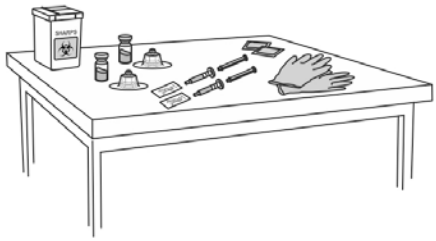
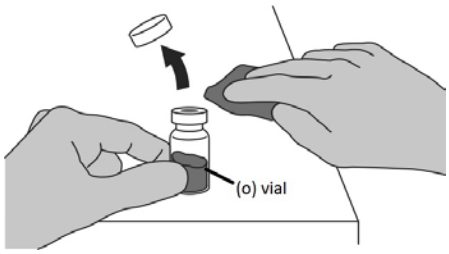
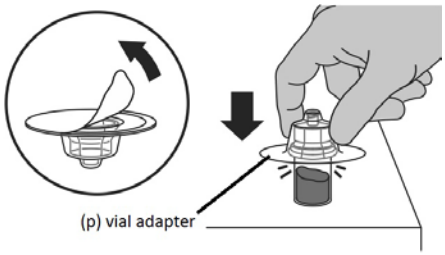
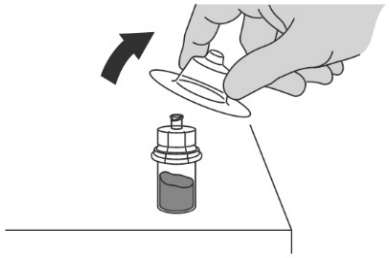
- Reconstituted drug must be administered within **one hour** after addition of Sterile Water for Injection, USP.
- Do not shake the vials.

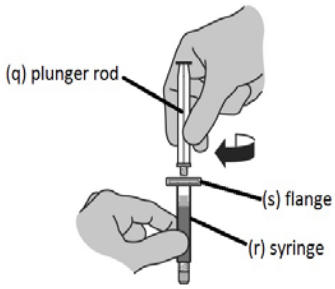
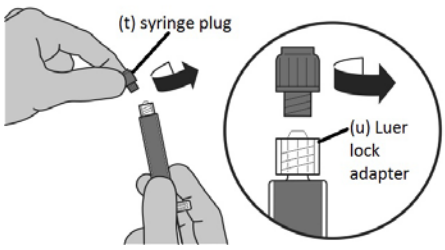
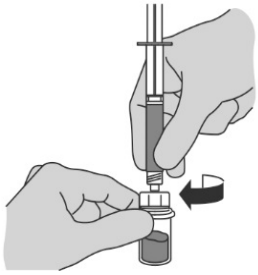
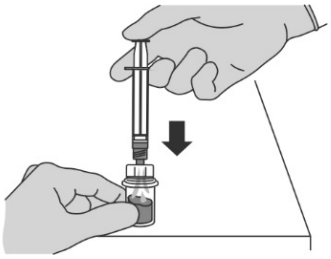
Follow aseptic technique.

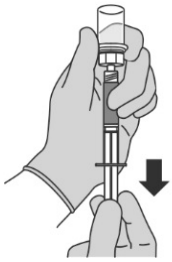
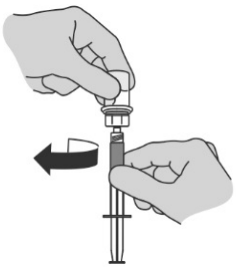
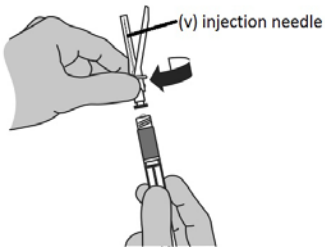
	**FIRMAGON 240 mg Starting Dose Kit contains:** • 2 vials containing the **120** mg FIRMAGON® powder (a) • 2 syringes containing Sterile Water for Injection, USP (b) • 2 vial adapters (c) • 2 injection needles (d) • 2 plunger rods (e)
	**FIRMAGON 80 mg Maintenance Dose Kit contains:** • 1 vial containing the **80** mg FIRMAGON® powder (f) • 1 syringe containing Sterile Water for Injection, USP (g) • 1 vial adapter (h) • 1 injection needle (i) • 1 plunger rod (j)
	**In addition the healthcare professional will need:** • gloves (k) • alcohol pads (l) • a clean, flat surface (m) to work on, like a table • a sharps disposal container (n) for throwing away your used needles and syringes. See “Disposing used needles and syringes” at the end of these instructions.

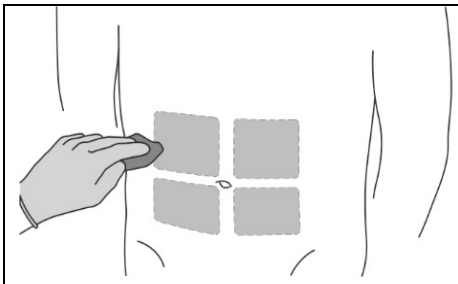
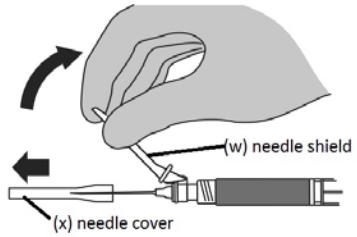
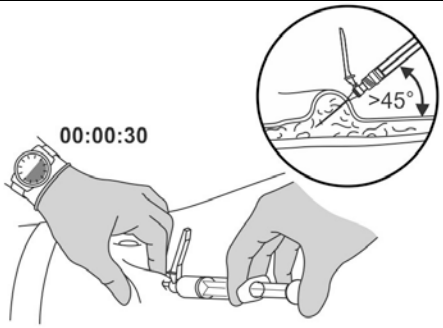
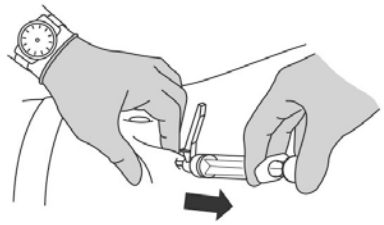
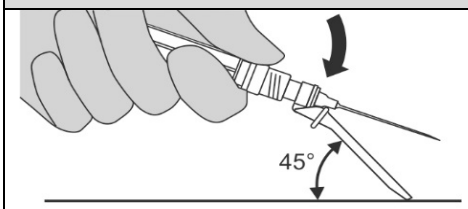
The drug product must be prepared using the following instructions:

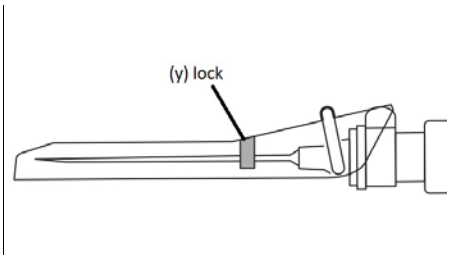
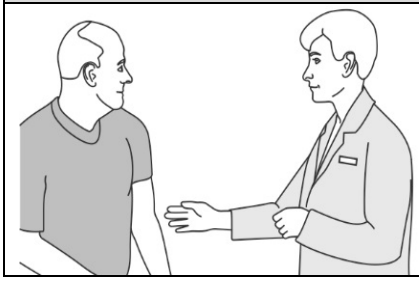
NOTE: *The mixing process must be repeated for the two injections of the Starting Dose prior to injecting the product into the patient's abdomen.*

	**Step 1: Attaching the vial adaptor to the vial** • Thoroughly wash your hands using soap and water and put on a pair of clean gloves. • Place all the supplies required on a clean surface. • Check that there is powder in the FIRMAGON® vial and that the Sterile Water, USP is clear and free from particles. ***IMPORTANT:*** *DO NOT USE if there is no powder in the vial or the Sterile Water, USP is discolored.*
	• Uncap the vial containing the FIRMAGON powder (o). • Wipe the vial rubber stopper with an alcohol pad. ***IMPORTANT:*** *Do not touch the top of the vial after wiping.*
	• Peel off the seal from the vial adaptor cover. ***IMPORTANT:*** *Do not touch the vial adapter.* • Firmly press the vial adaptor (p) onto the vial containing the FIRMAGON® powder until the adaptor snaps into place.
	• Pull the vial adaptor cover off the vial.

	**Step 2: Assembling the syringe** • Insert the plunger rod (q) into the prefilled syringe containing Sterile Water, USP (r) and **screw** the plunger rod clockwise to tighten. ***IMPORTANT:*** *Do not pull the back stopper (flange) (s) off the syringe.* ***NOTE:*** *You will only feel light resistance screwing the plunger rod in position.*
	**Step 3: Transferring sterile water, USP from the syringe to the vial** • **Unscrew** the gray syringe plug (t) attached to the Luer lock adaptor on the syringe. ***IMPORTANT: Do not*** *pull off the Luer lock adaptor (u).*
	• Carefully twist the prefilled syringe containing sterile water, USP onto the vial adapter on the FIRMAGON® powder vial, until it is tight. ***IMPORTANT:*** *Be careful not to over twist the syringe.*
	• Press the plunger slowly to transfer all the sterile water, USP from the syringe to the FIRMAGON® powder vial.

	**Step 4: Preparing the reconstituted injection** • With the syringe still attached to the vial adaptor, swirl **gently until the liquid is clear with no powder or visible particles**. ***IMPORTANT:*** • **Do not shake** the vial as this will cause bubbles. • **Reconstitute just prior to administration.** ***NOTE****: If the powder adheres to the side of the vial, tilt the vial slightly. A ring of small air bubbles on the surface of the liquid is acceptable.* *Reconstitution time can take up to 15 min but usually takes a few minutes.*
	**Step 5: Transferring the liquid to the syringe** • Turn the vial completely upside down and pull down the plunger to **withdraw all of the reconstituted liquid from the vial to the syringe.** • Tap the syringe gently with your fingers to raise air bubbles in the syringe tip. • Press the plunger to the line marked on the syringe to expel all air bubbles.
	**Step 6: Preparing the syringe for injection** • Holding the vial adaptor detach the syringe from the vial by unscrewing the syringe from the vial adaptor. ***NOTE****: Reconstitute just prior to administration.*
	• While holding the syringe with the tip pointing up, screw the injection needle (v) clockwise (right) onto the syringe.

	**Step 7: Preparing the patient** • Select one of the four available injection sites on the abdomen. ***IMPORTANT:*** o *Do not inject in areas where the patient will be exposed to pressure, such as area around the belt of the waistband or close to the ribs.* o *Vary the injection site periodically during treatment to minimize discomfort to the patient.* • Clean the injection site with an alcohol pad.
	**Step 8: Performing the injection** • Move the needle shield (w) away from the needle and carefully remove the needle cover (x).
	• **Pinch and elevate the skin** of the abdomen. • Insert the needle into the skin **<u>at a 45 degree</u> angle <u>all the way</u> to the hub**. • Do not inject into a vein or muscle. Gently pull back the plunger to check if blood is aspirated. ***IMPORTANT:*** *If blood appears in the syringe, the product should not be injected. Discontinue the injection and discard the syringe and the needle (reconstitute a new dose for the patient).* • Perform a **<u>slow</u>,** deep subcutaneous **injection over 30 seconds.**
	• **Remove the needle <u>and then</u> release the skin.** ***IMPORTANT:*** *Do not rub the injection site after retracting the needle.*
	**Step 9: Locking the needle into the shield** • Position the needle shield approximately 45 degrees to a flat surface. • Press down with a firm, quick motion until a distinct, audible “click” is heard.

	• Visually confirm that the needle is fully engaged under the lock (y). ***IMPORTANT:*** *Syringe is for single use only. Do not reuse the syringe and needle.*
	**Step 10: Advising the patient** • Instruct the patient not to rub or scratch the injection site. • Inform that some patients may feel a lump at the injection site and experience redness, soreness and discomfort for a few days after the injection.

Disposing used needles and syringes

- Put used alcohol swabs, needles and syringes in an FDA-cleared sharps disposal container right away after use. **Do not throw away loose needles and syringes in the trash.**
- For more information about safe sharps disposal, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.

3 DOSAGE FORMS AND STRENGTHS

Starting dose

One starting dose comprises 240 mg given as two 3 mL injections of 120 mg each.

Powder for injection 120 mg:

One vial of FIRMAGON 120 mg contains 120 mg degarelix. Each vial is to be reconstituted with a prefilled syringe containing 3 mL of Sterile Water for Injection. 3 mL is withdrawn to deliver 120 mg degarelix at a concentration of 40 mg/mL.

Maintenance dose

One maintenance dose comprises 80 mg given as one 4 mL injection.

Powder for injection 80 mg:

One vial of FIRMAGON 80 mg contains 80 mg degarelix. Each vial is to be reconstituted with a prefilled syringe containing 4.2 mL of Sterile Water for Injection. 4 mL is withdrawn to deliver 80 mg degarelix at a concentration of 20 mg/mL.

4 CONTRAINDICATIONS

FIRMAGON is contraindicated in patients with known hypersensitivity to degarelix or to any of the product components. *[see Warnings and Precautions (5.2)]*.

Degarelix is contraindicated in women who are or may become pregnant. Degarelix can cause fetal harm when administered to a pregnant woman. Degarelix given to rabbits during organogenesis at doses that were 0.02% of the clinical loading dose (240 mg) on a mg/m^2 basis caused embryo/fetal lethality and abortion. When degarelix was given to female rats during organogenesis, at doses that were just 0.036% of the clinical loading dose on an mg/m^2 basis, there was an increase post implantation loss and a decrease in the number of live fetuses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

5 WARNINGS AND PRECAUTIONS

5.1 Use in Pregnancy

Pregnancy Category X

Women who are or may become pregnant should not take FIRMAGON *[see Contraindications (4) and Use in Specific Populations (8.1)]*.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, urticaria and angioedema, have been reported post-marketing with Firmagon. In case of a serious hypersensitivity reaction, discontinue Firmagon immediately if the injection has not been completed, and manage as clinically indicated. Patients with a known history of serious hypersensitivity reactions to Firmagon should not be re-challenged with Firmagon.

5.3 Effect on QT/QTc Interval

Androgen deprivation therapy may prolong the QT interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

In the randomized, active-controlled trial comparing FIRMAGON to leuprolide, periodic electro-cardiograms were performed. Seven patients, three (<1%) in the pooled degarelix group and four (2%) patients in the leuprolide 7.5 mg group, had a QTcF ≥ 500 msec. From baseline to end of study, the median change for FIRMAGON was 12.3 msec and for leuprolide was 16.7 msec.

5.4 Laboratory Testing

Therapy with FIRMAGON results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after FIRMAGON may be affected. The therapeutic effect of FIRMAGON should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 1325 patients with prostate cancer received FIRMAGON either as a monthly treatment (60-160 mg) or as a single dose (up to 320 mg). A total of 1032 patients (78%) were treated for at least 6 months and 853 patients (64%) were treated for one year or more. The most commonly observed adverse reactions during FIRMAGON therapy included injection site reactions (e.g., pain, erythema, swelling or induration), hot flashes, increased weight, fatigue, and increases in serum levels of transaminases and gamma-glutamyltransferase (GGT). The majority of the adverse reactions were Grade 1 or 2, with Grade 3/4 adverse reaction incidences of 1% or less.

FIRMAGON was studied in an active-controlled trial (N = 610) in which patients with prostate cancer were randomized to receive FIRMAGON (subcutaneous) or leuprolide (intramuscular) monthly for 12 months. Adverse reactions reported in 5% of patients or more are shown in Table 1.

Table 1. Adverse Reactions Reported in ≥ 5% of Patients in an Active Controlled Study

	FIRMAGON 240/160 mg (subcutaneous) N = 202	FIRMAGON 240/80 mg (subcutaneous) N = 207	Leuprolide 7.5 mg (intramuscular) N = 201
Percentage of subjects with adverse events	83%	79%	78%
Body as a whole			
Injection site adverse events	44%	35%	<1%
Weight increase	11%	9%	12%
Fatigue	6%	3%	6%
Chills	4%	5%	0%
Cardiovascular system			
Hot flash	26%	26%	21%
Hypertension	7%	6%	4%
Musculoskeletal system			
Back pain	6%	6%	8%
Arthralgia	4%	5%	9%
Urogenital system			
Urinary tract infection	2%	5%	9%
Digestive system			
Increases in Transaminases and GGT	10%	10%	5%
Constipation	3%	5%	5%

The most frequently reported adverse reactions at the injection sites were pain (28%), erythema (17%), swelling (6%), induration (4%) and nodule (3%). These adverse reactions were mostly transient, of mild to moderate intensity, occurred primarily with the starting dose and led to few discontinuations (<1%). Grade 3 injection site reactions occurred in 2% or less of patients receiving degarelix.

Hepatic laboratory abnormalities were primarily Grade 1 or 2 and were generally reversible. Grade 3 hepatic laboratory abnormalities occurred in less than 1% of patients.

In 1-5% of patients the following adverse reactions, not already listed, were considered related to FIRMAGON by the investigator:

Body as a whole: Asthenia, fever, night sweats; *Digestive system:* Nausea; *Nervous system:* Dizziness, headache, insomnia.

The following adverse reactions, not already listed, were reported to be drug-related by the investigator in ≥1% of patients: erectile dysfunction, gynecomastia, hyperhidrosis, testicular atrophy, and diarrhea.

The safety of FIRMAGON administered monthly was evaluated further in an extension study in 385 patients who completed the above active-controlled trial. Of the 385 patients, 251 patients continued treatment with FIRMAGON and 135 patients crossed over treatment from leuprolide to FIRMAGON. The median treatment duration on the extension study was approximately 43 months (range 1 to 58 months). The most common adverse reactions reported in ≥10% of the patients were injection site reactions (e.g., pain, erythema, swelling, induration or inflammation), pyrexia, hot flush, weight loss or gain, fatigue, increases in serum levels of hepatic transaminases and GGT. One percent of patients had injection site infections including abscess. Hepatic laboratory abnormalities in the extension study included the following: Grade 1/2 elevations in hepatic transaminases occurred in 47% of patients and Grade 3 elevations occurred in 1% of patients.

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 medical castration in men will result in decreased bone density.

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.

7 DRUG INTERACTIONS

No drug-drug interaction studies were conducted.

Degarelix is not a substrate for the human CYP450 system. Degarelix is not an inducer or inhibitor of the CYP450 system *in vitro*. Therefore, clinically significant CYP450 pharmacokinetic drug-drug interactions are unlikely.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category X *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Women who are or may become pregnant should not take FIRMAGON.

When degarelix was given to rabbits during early organogenesis at doses of 0.002 mg/kg/day (about 0.02% of the clinical loading dose on a mg/m^2 basis), there was an increase in early post-implantation loss. Degarelix given to rabbits during mid and late organogenesis at doses of 0.006 mg/kg/day (about 0.05% of the clinical loading dose on a mg/m^2 basis) caused embryo/fetal lethality and abortion. When degarelix was given to female rats during early organogenesis, at doses of 0.0045 mg/kg/day (about 0.036% of the clinical loading dose on a mg/m^2 basis), there was an increase in early post-implantation loss. When degarelix was given to female rats during mid and late organogenesis, at doses of 0.045 mg/kg/day (about 0.36% of the clinical loading dose on a mg/m^2 basis), there was an increase in the number of minor skeletal abnormalities and variants.

8.3 Nursing Mothers

FIRMAGON is not indicated for use in women and is contraindicated in women who are or who may become pregnant. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from degarelix, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of FIRMAGON, 82% were age 65 and over, while 42% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No pharmacokinetic studies in renally impaired patients have been conducted. At least 20-30% of a given dose of degarelix is excreted unchanged in the urine.

A population pharmacokinetic analysis of data from the randomized study demonstrated that there is no significant effect of mild renal impairment [creatinine clearance (CrCL) 50-80 mL/min] on either the degarelix concentration or testosterone concentration. Data on patients with moderate or severe renal impairment is limited and therefore degarelix should be used with caution in patients with CrCL < 50 mL/min.

8.7 Hepatic Impairment

Patients with hepatic impairment were excluded from the randomized trial.

A single dose of 1 mg degarelix administered as an intravenous infusion over 1 hour was studied in 16 non-prostate cancer patients with either mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Compared to non-prostate cancer patients with normal liver function, the exposure of degarelix decreased by 10% and 18% in patients with mild and moderate hepatic impairment, respectively. Therefore, dose adjustment is not necessary in patients with mild or moderate hepatic impairment. However, since hepatic impairment can lower degarelix exposure, it is recommended that in patients with hepatic impairment testosterone concentrations should be monitored on a monthly basis until medical castration is achieved. Once medical castration is achieved, an every-other-month testosterone monitoring approach could be considered.

Patients with severe hepatic dysfunction have not been studied and caution is therefore warranted in this group.

10 OVERDOSAGE

There have been no reports of overdose with FIRMAGON. In the case of overdose, however, discontinue FIRMAGON, treat the patient symptomatically, and institute supportive measures.

As with all prescription drugs, this medicine should be kept out of the reach of children.

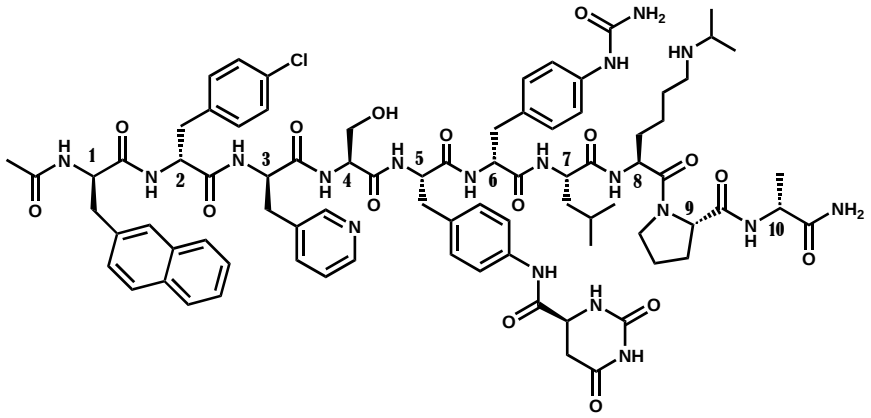
SEE FIRMAGON PATIENT COUNSELING INFORMATION

11 DESCRIPTION

FIRMAGON is a sterile lyophilized powder for injection containing degarelix (as the acetate) and mannitol. Degarelix is a synthetic linear decapeptide amide containing seven unnatural amino acids, five of which are D-amino acids. The acetate salt of degarelix is a white to off-white amorphous powder of low density as obtained after lyophilization.

The chemical name of degarelix is D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[[(4S)-hexahydro-2,6-dioxo-4-pyrimidinyl]carbonyl]amino]-L phenylalanyl-4-[(aminocarbonyl)amino]-D-phenylalanyl-L leucyl-N6–(1-methylethyl)-L-lysyl-L-prolyl. It has an empirical formula of $C_{82}H_{103}N_{18}O_{16}Cl$ and a molecular weight of 1632.3 Da.

Degarelix has the following structural formula:



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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

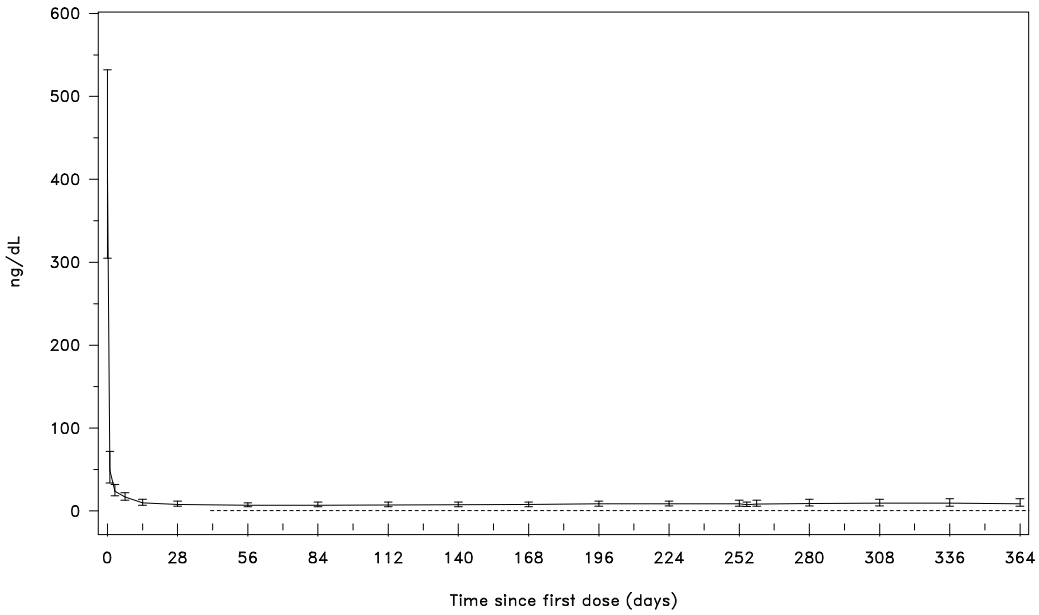
Degarelix is a GnRH receptor antagonist. It binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone.

12.2 Pharmacodynamics

A single dose of 240 mg FIRMAGON causes a decrease in the plasma concentrations of luteinizing hormone (LH) and follicle stimulating hormone (FSH), and subsequently testosterone.

FIRMAGON is effective in achieving and maintaining testosterone suppression below the castration level of 50 ng/dL.

Figure 1: Plasma Testosterone Levels from Day 0 to 364 for Degarelix 240 mg/80 mg (Median with Interquartile Ranges)



12.3 Pharmacokinetics

Absorption

FIRMAGON forms a depot upon subcutaneous administration, from which degarelix is released to the circulation. Following administration of FIRMAGON 240 mg at a product concentration of 40 mg/mL, the mean Cmax was 26.2 ng/mL (coefficient of variation, CV 83%) and the mean AUC was 1054 ng·day/mL (CV 35%). Typically Cmax occurred within 2 days after subcutaneous administration. In prostate cancer patients at a product concentration of 40 mg/mL, the pharmacokinetics of degarelix were linear over a dose range of 120 to 240 mg. The pharmacokinetic behavior of the drug is strongly influenced by its concentration in the injection solution.

Distribution

The distribution volume of degarelix after intravenous (> 1 L/kg) or subcutaneous administration (> 1000L) indicates that degarelix is distributed throughout total body water. *In vitro* plasma protein binding of degarelix is estimated to be approximately 90%.

Metabolism

Degarelix is subject to peptide hydrolysis during the passage of the hepato-biliary system and is mainly excreted as peptide fragments in the feces. No quantitatively significant metabolites were detected in plasma samples after subcutaneous administration. *In vitro* studies have shown that degarelix is not a substrate, inducer or inhibitor of the CYP450 or p-glycoprotein transporter systems.

Excretion

Following subcutaneous administration of 240 mg FIRMAGON at a concentration of 40 mg/mL to prostate cancer patients, degarelix is eliminated in a biphasic fashion, with a median terminal half-life of approximately 53 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). 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. Following subcutaneous administration of degarelix to prostate cancer patients the clearance is approximately 9 L/hr.

Effect of Age, Weight and Race

There was no effect of age, weight or race on the degarelix pharmacokinetic parameters or testosterone concentration.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Degarelix was administered subcutaneously to rats every 2 weeks for 2 years at doses of 2, 10 and 25 mg/kg (about 9, 45 and 120% of the recommended human loading dose on a mg/m^2 basis). Long term treatment with degarelix at 25 mg/kg caused an increase in the combined incidence of benign hemangiomas plus malignant hemangiosarcomas in females.

Degarelix was administered subcutaneously to mice every 2 weeks for 2 years at doses of 2, 10 and 50 mg/kg (about 5, 22 and 120% of the recommended human loading dose (240 mg) on a mg/m^2 basis). There was no statistically significant increase in tumor incidence associated with this treatment.

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.

Single degarelix doses of $\geq$ 1 mg/kg (about 5% of the clinical loading dose on a mg/m^2 basis) caused reversible infertility in male rats. Single doses of $\geq$ 0.1 mg/kg (about 0.5% of the clinical loading dose on a mg/m^2 basis) caused a decrease in fertility in female rats.

14 CLINICAL STUDIES

The safety and efficacy of FIRMAGON were evaluated in an open-label, multi-center, randomized, parallel-group study in patients with prostate cancer. A total of 620 patients were randomized to receive one of two FIRMAGON dosing regimens or leuprolide for one year:

a. FIRMAGON at a starting dose of 240 mg (40 mg/mL) followed by monthly doses of 160 mg (40 mg/mL) subcutaneously,
b. FIRMAGON at a starting dose of 240 mg (40 mg/mL) followed by monthly doses of 80 mg (20 mg/mL) subcutaneously,
c. leuprolide 7.5 mg intramuscularly monthly.

Serum levels of testosterone were measured at screening, on Day 0, 1, 3, 7, 14, and 28 in the first month, and then monthly until the end of the study.

The clinical trial population (n=610) across all treatment arms had an overall median age of approximately 73 (range 50 to 98). The ethnic/racial distribution was 84% white, 6% black and 10% others. Disease stage was distributed approximately as follows: 20% metastatic, 29% locally advanced (T3/T4 Nx M0 or N1 M0), 31% localized (T1 or T2 N0 M0) and 20% classified as other (including patients whose disease metastatic status could

not be determined definitively - or patients with PSA relapse after primary curative therapy). In addition, the median testosterone baseline value across treatment arms was approximately 400 ng/dL.

The primary objective was to demonstrate that FIRMAGON is effective with respect to achieving and maintaining testosterone suppression to castration levels (T ≤ 50 ng/dL), during 12 months treatment. The results are shown in Table 2.

Table 2: Medical Castration Rates (Testosterone ≤ 50 ng/dL) from Day 28 to Day 364

	FIRMAGON 240/160 mg N=202	**FIRMAGON 240/80 mg N=207**	**Leuprolide 7.5 mg N=201**
No. of Responders	199	202	194
Castration Rate (95% CIs)*	98.3% (94.8; 99.4)	97.2% (93.5; 98.8)	96.4% (92.5; 98.2)

* Kaplan Meier estimates within group

Percentage changes in testosterone from baseline to Day 28 (median with interquartile ranges) are shown in Figure 2 and the percentages of patients who attained the medical castration of testosterone ≤ 50 ng/dL are summarized in Table 3.

Figure 2: Percentage Change in Testosterone from Baseline by Treatment Group until Day 28 (Median with Interquartile Ranges)

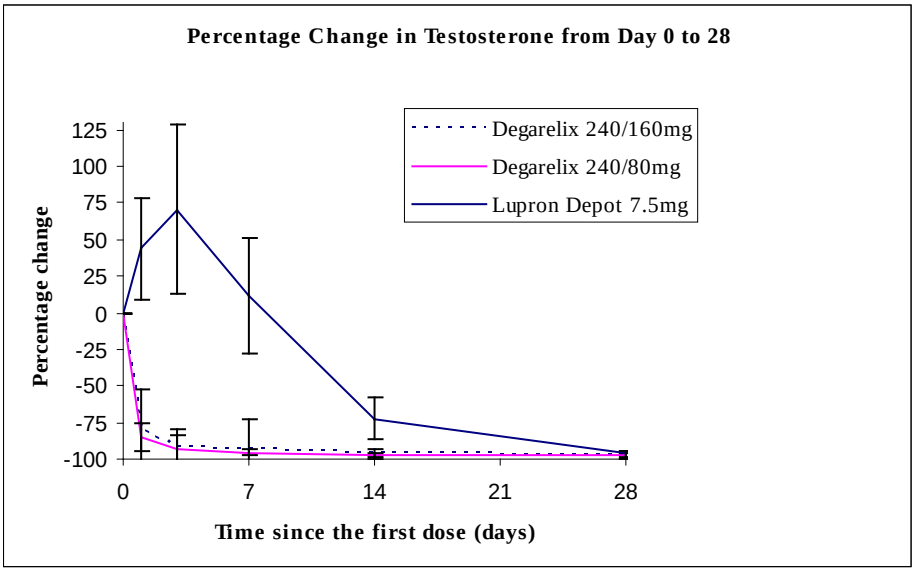


Table 3: Percentage of Patients Attaining Testosterone ≤ 50 ng/dL within the First 28 Days

	FIRMAGON 240/160 mg N=202	FIRMAGON 240/80 mg N=207	Leuprolide 7.5 mg N=201
Day 1	44%	52%	0%
Day 3	96%	96%	0%
Day 7	99%	99%	1%
Day 14	99%	99%	18%
Day 28	99%	100%	100%

In the clinical trial, PSA levels were monitored as a secondary endpoint. PSA levels were lowered by 64% two weeks after administration of FIRMAGON, 85% after one month, 95% after three months, and remained suppressed throughout the one year of treatment. These PSA results should be interpreted with caution because of the heterogeneity of the patient population studied. No evidence has shown that the rapidity of PSA decline is related to a clinical benefit.

16 HOW SUPPLIED/STORAGE AND HANDLING

FIRMAGON is available as:

- NDC 55566-8403-1, Starting dose – One carton contains:
  Two vials each with 120 mg powder for injection
  Two prefilled syringes containing 3 mL of sterile water for injection, USP
  Two vial adapters
  Two administration needles

- NDC 55566-8303-1, Maintenance dose – One carton contains:
  One vial with 80 mg powder for injection
  One prefilled syringe containing 4.2 mL of sterile water for injection, USP
  One vial adapter
  One administration needle

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Discard all components safely in an appropriate biohazard container.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

- Patients should be informed of the possible side effects of androgen deprivation therapy, including hot flashes, flushing of the skin, increased weight, decreased sex drive, and difficulties with erectile function. Possible side effects related to therapy with FIRMAGON include redness, swelling, and itching at the injection site; these are usually mild, self limiting, and decrease within three days.

Manufactured for:
Ferring Pharmaceuticals Inc., Parsippany, NJ 07054
By: Rentschler Biotechnologie GmbH, Germany

2009054134
Rev. 10/2015

Patient Information
FIRMAGON (FIRM-uh-gahn)
(degarelix for injection)

What is FIRMAGON?
FIRMAGON is a prescription medicine used in the treatment of advanced prostate cancer.
It is not known if FIRMAGON is safe or effective in children.

Who should not receive FIRMAGON?
Do not receive FIRMAGON if you are:
- allergic to degarelix or any ingredient in FIRMAGON. See the end of this leaflet for a complete list of ingredients in FIRMAGON.
- a female who is pregnant or may become pregnant. FIRMAGON can harm your unborn baby.

Talk to your healthcare provider before receiving FIRMAGON if you have any of these conditions.

Before receiving FIRMAGON, tell your healthcare provider about all your medical conditions, including if you:
- have any heart problems including a condition called long QT syndrome.
- have problems with blood levels such as sodium, potassium, calcium, and magnesium
- have kidney or liver problems
- are breastfeeding or plan to breastfeed. It is not known if FIRMAGON passes into your breast milk. You and your healthcare provider should decide if you will receive FIRMAGON or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

How will I receive FIRMAGON?
You will receive an injection of FIRMAGON from your healthcare provider.
- The injection site will always be in the stomach (abdominal area). The injection site will change within the stomach area each time you receive a dose of FIRMAGON.
- Two injections are given as a first dose. The following monthly doses are one injection.
- Do not rub or scratch the injection site. Make sure your injection site is free of any pressure from belts, waistbands or other types of clothing.
- Always set up an appointment for your next injection.

What are the possible side effects of FIRMAGON?
FIRMAGON can cause serious side effects, including:
- **Serious allergic reactions.** Get medical help right away if you get any of these symptoms:
  - trouble breathing or wheezing
  - swelling of your face, lips, mouth, or tongue
  - severe itching
- **Disorder of the heart's electrical activity.** Your healthcare provider may do tests during treatment with FIRMAGON to check your heart for a condition called long QT syndrome.

The common side effects of FIRMAGON include:
- injection site pain, redness, and swelling
- hot flashes
- weight gain
- increase in some liver enzymes

Other side effects include decreased sex drive and erectile function problems.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of FIRMAGON.
Medicines are sometimes prescribed for conditions that are not mentioned in a Patient Information leaflet. Do not use FIRMAGON for a condition for which it was not prescribed. Do not give FIRMAGON to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your pharmacist or healthcare provider for information about FIRMAGON that is written for health professionals.

What are the ingredients in FIRMAGON?
Active ingredient: degarelix (as acetate)
Inactive ingredient: mannitol

Manufactured for: Ferring Pharmaceuticals Inc., Parsippany, NJ 07054
By: Rentschler Biotechnologie GmbH, Germany
For more information, go to www.FIRMAGON.com or call -1-888-337-7464.

FERRING
PHARMACEUTICALS

This Patient Information has been approved by the U.S. Food and Drug Adminstration.

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