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FIRMAGON[®] (degarelix for injection) *For Advanced Prostate Cancer Treatment*

FIRMAGON[®] (degarelix for injection), is the only available gonadotropin-releasing hormone (GnRH) receptor antagonist approved by the FDA for the treatment of patients with advanced prostate cancer. Developed by **Ferring Pharmaceuticals (Parsippany, NJ)**, FIRMAGON[®] achieves medical castration differently than GnRH or luteinizing hormone-releasing hormone (LHRH) agonists, specifically by binding reversibly to GnRH receptors on cells in the pituitary gland, quickly reducing the release of gonadotropins and consequently testosterone.^{1,2,3,4} FIRMAGON[®] has been shown to achieve rapid and sustained reduction in testosterone levels to below castrate level (≤ 50 ng/dL) within 3 days, with no testosterone surge.^{1,2}

It has been generally recognized that prostate cancer has a high sensitivity to testosterone deprivation and suppressing the production of testosterone inhibits tumor growth.^{5,6} "It is generally important to get testosterone levels down quickly in a patient with advanced prostate cancer, because you want a rapid affect on the disease," notes Judd W. Moul, MD, Chief, Division of Urologic Surgery, and Director, Duke Prostate Center, Duke University Medical Center (Durham, NC). "FIRMAGON's unique mechanism of action almost immediately causes testosterone levels to go below castrate levels. Typically, with FIRMAGON you will get patients to a castrate level of testosterone within 3 days, whereas with an [LHRH] agonist, it can take up to 30 days."

Dr. Moul says that LHRH agonists have been a key part of the physicians' armamentarium to treat patients with advanced prostate cancer. "However, not only do these agonists have a slower effect on reducing testosterone to castrate levels, the mechanism of action for these agonists also temporarily *increases* testosterone levels." Dr. Moul explains that this initial short-term surge in testosterone levels not only leads to a delay in therapeutic benefit, but can also be associated with clinical flare, which can aggravate the hormone-sensitive cancer and patient symptoms. The rapid decrease in testosterone production with FIRMAGON avoids the side effects of flare while allowing for immediate inhibition of tumor growth. Symptoms of flare can include sudden paraplegia due to spinal cord compression by epidural metastases, exacerbation of bone pain, and urinary retention.⁷ Anti-androgens are often administered simultaneously as a "flare blockade" in the beginning stage of receptor agonist treatment to help decrease the stimulatory effects of the testosterone surge.⁵

A 12-month, randomized, open-label, parallel group Phase III study evaluated the efficacy and safety of degarelix (FIRMAGON[®]) compared with leuprolide (Lupron Depot[®]), administered monthly over one year of prostate cancer treatment. The study demonstrated that degarelix was at least as effective as leuprolide in sustaining castrate levels over 12 months providing primary evidence that degarelix is an effective therapy for inducing and maintaining androgen deprivation.¹ At day three of treatment, 96% of degarelix patients achieved castrate levels of testosterone, compared with zero percent of those receiving leuprolide. By day fourteen, 99% of degarelix patients achieved castrate levels of testosterone, compared with 18% receiving leuprolide. By day 28, patients in both treatment arms achieved castrate levels of testosterone. In the clinical trial, PSA levels were also monitored as a secondary endpoint. PSA levels were lowered by 64% two weeks after administration of degarelix, 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.¹ 



For more information about Degarelix, please call 1-888-FERRING, visit www.FIRMAGON.com.

References:

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Brief Summary—See Package Insert for Full Prescribing Information.

FIRMAGON® (degarelix for injection)
Rx Only

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

FIRMAGON is contraindicated in patients with known hypersensitivity to degarelix or to any of the product components.

FIRMAGON 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/m² 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 a mg/m² 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.

WARNINGS AND PRECAUTIONS

Use in Pregnancy: Pregnancy Category X: Women who are or may become pregnant should not take FIRMAGON.

Effect on QT/QTc Interval: Long-term androgen deprivation therapy prolongs the QT interval. Physicians should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure and in patients taking Class IA (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications. In the randomized, active-controlled trial comparing FIRMAGON to leuprolide, periodic electrocardiograms were performed. Seven patients, three (<1%) in the pooled degarelix group and four (2%) in the leuprolide 7.5 mg group, had a QTcF ≥500 ms. From baseline to end of study the median change for FIRMAGON was 12.3 msec and for leuprolide was 16.7 msec.

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.

ADVERSE REACTIONS

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 gammaglutamyltransferase (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%
<i>Body as a whole</i>			
Injection site adverse events	44%	35%	<1%
Weight increase	11%	9%	12%
Fatigue	6%	3%	6%
Chills	4%	5%	0%
<i>Cardiovascular system</i>			
Hot flash	26%	26%	21%
Hypertension	7%	6%	4%
<i>Musculoskeletal system</i>			
Back pain	6%	6%	8%
Arthralgia	4%	5%	9%
<i>Urogenital system</i>			
Urinary tract infection	2%	5%	9%
<i>Digestive system</i>			
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.

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.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy: Category X

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/m² 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/m² 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/m² 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/m² basis), there was an increase in the number of minor skeletal abnormalities and variants.

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.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

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.

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.

Hepatic Impairment: Patients with severe hepatic dysfunction 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.

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.

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

