CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-201

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	December 24, 2008
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-201
Applicant Name	Ferring Pharmaceuticals Inc.
Date of Submission	February 29, 2008
PDUFA Goal Date	December 28, 2008
Proprietary Name / **Established (USAN) Name**	Proprietary name is pending/ Degarelix for injection
Dosage Forms / Strength	Powder for injection, 120 mg and 80 mg vials
Proposed Indication(s)	Treatment of patients with advanced prostate cancer.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	X
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	
DSI	X
CDTL Review	N/A
OSE/DMEPA	X
OSE/DDRE	N/A
OSE/DRISK	X
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

This new drug application was submitted on February 29, 2009 for the indication of "treatment of patients with prostate cancer ———————————— The application was given a standard review. This review will summarize the study design, safety and efficacy results, and the conclusions and recommendations of each review discipline. This review will also serve as the cross-discipline team leader review.

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2. Background

Degarelix is a competitive inhibitor of the GnRH receptor. It binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone. Sustained suppression of testosterone to castrate levels (≤50 ng/dL) has been accepted by the Agency as an established surrogate of clinical benefit in the treatment of patients with advanced prostate cancer and has been the basis for approval of GnRH receptor agonists and another GnRH receptor antagonist.

3. CMC/Device

The initial Chemistry Review of 12/23/08 recommended approval pending resolution of labeling issues. The labeling issues were resolved and the final Chemistry Review of 12/24/08 had the following recommendations.

A. Recommendation and Conclusion on Approvability

The application is recommended for an approvable action by ONDQA for manufacturing and controls under Section 505 of the Act.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

The ONDQA Division Director's memo stated that "A recommendation for approval (AP) from ONDQA is recommended."

The Product Quality Microbiology Review recommended approval.

Comment: I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review and Evaluation provided the following overview of nonclinical findings.

> Degarelix binds to the isolated human GnRH receptor with an affinity (k_i) of about 1.7 nM. The inhibition of the GnRH receptor prevents the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) form the pituitary gland. This results in a significant decrease in testosterone or estradiol release. The effect of this inhibition is rapid. Single subcutaneous doses of degarelix as low as 1-μg/kg caused a significant decrease in plasma testosterone in male rats six hours after the injection. The degree of testosterone suppression increases with increasing dose. This decrease in testosterone was accompanied by aspermia, derangement of sperm morphology and loss of fertility. The lack of stimulation by circulating testosterone results in atrophy in the prostate, testes and epididymides that increased in severity with increasing dose. The time to recovery of reproductive function in males also increased with increasing dose and total time of exposure. This decrease in testosterone is the desired clinical effect and the primary endpoint of the clinical study. Treatment with degarelix also caused a rapid decrease in plasma concentrations of estradiol in all species studied secondary to the inhibition of the release of LH and FSH. This decrease resulted in sporadic or infrequent estrus or complete amenorrhea depending on the dose and the total time of exposure. Recovery of reproductive function in females was somewhat faster than it was in males probably because testicular atrophy was somewhat worse than atrophy in the female sex organs after treatment. These decreases in estradiol cause weight increases in treated female animals and weight decreases in treated male animals.
>
> Single SC doses as high as 300 mg/m^2 caused no neurological or behavioral changes in mice, but the same dose given to mice IV rapidly led to death preceded by signs of neurological toxicity including unsteady gate, hyperactivity and pallid brain tissue on gross examination.
>
> Degarelix interacts with the baroreceptor and at high IV doses in the dog causes unusual and severe changes in arterial blood pressure that do not correlate with C_{max}. Other changes in cardiac parameters suggest the possibility of mild chronic cardiac toxicity that may affect contractility. This cardiac toxicity is not completely characterized. The implications for patients with congestive failure, frequent orthostatic hypotension, chronic renal failure or other heart related conditions remain unknown.
>
> Red and white blood cell counts varied considerably in treated animals depending on dose, schedule and species. In most studies, male animals developed mild anemia and

both males and females developed neutrophilia. Changes in other parameters suggest possible mild renal and hepatic toxicity with chronic treatment.

Degarelix did not cause increases in bacterial mutations in six separate Ames assays either with or without metabolic activation. In six separate studies in L5178Y mouse lymphoma cells, degarelix caused no increase in mutations at the TK locus. In two separate *in vivo* studies, degarelix caused no increase in micronucleated immature rat erythrocytes. Thus, degarelix is not genotoxic under the conditions of standard *in vitro* or *in vivo* assays.

In a standard 24 month carcinogenicity study in rats where degarelix was given fortnightly (52 subcutaneous doses), the high dose of 150 mg/m^2 was about the same as the proposed clinical loading dose and about 3 times greater than the proposed monthly maintenance dose on a mg/m^2 basis. The mid dose was 60 mg/m^2 and the low dose was 12 mg/m^2. The incidence of benign adenoma of the pituitary gland decreased in all groups of treated females ($p < 0.02$). The incidence of benign fibroadenoma of the breast decreased in all groups of treated females ($p < 0.024$). These decreases were related to decreased stimulation of the pituitary and atrophy of both the pituitary and the mammary glands. The incidence of eosinophilic cell foci in the liver increased in low dose females ($p < 0.001$). Lastly, there was an increase in metastatic hemangiosarcoma of the mesenteric lymph node in HD females ($p < 0.04$, with a positive trend by Peto analysis $p = 0.015$). The incidence of this tumor was 8% which is within the range seen in historical controls. There was no similar finding in males. The combined incidence of all benign and malignant hemangiomas and hemangiosarcomas (16%) was significantly different from controls by pairwise comparison ($p = 0.0013$, Exact test) in the high dose group. This difference remained significant when analyzed by the asymptotic trend test ($p = 0.0008$).

In a standard 24 month carcinogenicity study in mice, treatment with degarelix at doses of 6, 30 and 150 mg/m^2 fortnightly for two years caused an increase in benign bronchio-alveolar adenoma in all groups of treated females ($p < 0.04$) when analyzed by pairwise comparison with control. When the incidence of benign bronchio-alveolar adenoma was combined with that of malignant bronchio-alveolar carcinoma the result was not statistically different from controls by pairwise comparison. The incidence of benign bronchio-alveolar adenoma in male CD-1 mice ranges from 11 to 36 %, in females it ranges from 3 to 16%. Dosing in this study also caused an increase in benign hepatocellular adenoma of the liver ($p = 0.015$) in high dose females. By trend analysis the increase in benign hepatocellular adenoma of the liver reached significance in both males ($p = 0.03$) and females ($p < 0.04$). When the incidence of benign hepatocellular adenoma was combined with that of malignant hepatocellular carcinoma the result was not significantly different from controls in males or females ($p < 0.09$) by pairwise comparison. The combined incidence of these tumors was also not statistically different from controls by asymptotic trend test ($p < 0.09$). The normal incidence of hepatocellular adenoma of the liver ranges from 2 to 33 % in male CD-1 mice and from 0 to 4% in females. The normal range for hepatocellular carcinoma ranges from 0 to 1.7 % in females and 0 to 6% in males.

Doses of 0.072 mg/m^2/day from day 6 through day 12 followed by doses of 0.18 mg/m^2/day caused significant post-implantation loss in pregnant rats (23.6 %) and a concomitant decrease in the number of live fetuses/dam. This dose caused no significant maternal toxicity and is only about 0.13% of the proposed clinical loading dose. Dosing was associated with an increase in the number of major abnormalities in the fetuses in the high dose group ($p < 0.05$) but most of these abnormalities occurred in a single litter (4 of 6). In fetuses in the mid dose group (0.54 mg/m^2/day followed by 0.18 mg/m^2/day at the schedule above) there was a statistically significant increase in a number of minor skeletal abnormalities and variants observed. These were findings generally associated with the state of ossification and were considered to be related to maternal treatment with Degarelix.

In rabbits, a daily dose of 0.024 mg/m^2 on days 6 through 14 followed by doses of 0.072 mg/m^2 from days 15 through 27 was associated with a decrease in the number of does with implantations, the number of corpora lutea per female, the number of implantations and the number of live fetuses per female. Some of these decreases reached statistical significance in the mid-high (0.12 mg/m^2/day followed by 0.36 mg/m^2/day at the schedule above) and high dose groups particularly the number of live fetuses. Dosing was also associated with an increase in mean post-implantation loss. There was an increase in the number of fetuses with minor abnormalities in the high dose group and an increase in the incidence of major abnormalities in the mid dose group (5 in three litters) but the number of fetuses in the high dose group was so diminished as to render any determination of teratogenicity equivocal. The high dose caused only minimal toxicity in the does (minimal decreased body weight gain). Thus, a daily dose of degarelix that was just 0.05% that of the proposed loading dose was a potent abortifacient in rabbits.

Single degarelix doses of $\geq$ 6 mg/m^2 (about 5% of the clinical loading dose on a mg/m^2 basis) caused reversible infertility in male rats. Single doses of = 0.6 mg/m^2 (about 0.5% of the clinical loading dose on a mg/m2 basis) caused a decrease in fertility in female rats.

When given as a relatively low IV dose in rats and monkeys, the two most often studied species in this NDA submission, the AUC increases linearly and proportionately with increasing dose and there was no evidence of accumulation. Terminal elimination half-life is about 5 hours in the monkey and 3 hours in the rat. In humans, half-life was at least twice as long. In the rat, clearance was 0.21 $\pm$ 0.04 L/kg/hr; while the volume of distribution was 0.9 $\pm$ 0.5 L/kg. Clearance and volume of distribution were less in the monkey. In humans, exposure also increased proportionally and linearly with dose after an IV dose. In healthy volunteers given a single IV dose of 1 mg of degarelix as a 1 hour infusion, clearance was 3.2 $\pm$ 0.5 L/hr and volume of distribution was 79 $\pm$ 17 L (about 1 L/kg).

Parameters derived from the toxicokinetic studies of degarelix given subcutaneously are not informative because the absorption of the drug from the subcutaneous depot is

rate limiting. The terminal elimination half-life thus reflects the absorption rate constant, but in many cases this could not be determined accurately because the dosing interval was considerably shorter than five half-lives. Thus, values for clearance and volume were unusually large and variable. In almost all cases, the increase in C_{max} and AUC was non-linear and far less than dose proportional and most repeat dose studies demonstrated significant accumulation. Plots of C_{trough} demonstrated consistent exposure above the value of k_i even at low doses.

Degarelix is excreted in both urine (20 to 40%) and feces (20 to 40%) and excretion is essentially complete after 48 hours. In monkeys, total radioactivity distributed in highest amounts to excretory organs with the highest concentrations in bile, small intestine, urinary bladder, kidney, and liver respectively at 6 hours. Relatively high concentrations were found in the pituitary, prostate and testes consistent with the drugs pharmacology. Concentrations greater than that found in plasma were found in the aorta, lachrymal gland, lung, skin and vena cava. Elimination from the aorta, bile, pituitary, vena cava, prostate, kidneys and adrenals was slower than elimination from plasma. Plasma protein binding is about 90% in humans.

In vitro evidence suggests that cytochrome P450 is not extensively involved in degarelix metabolism. Most metabolism is hydrolytic at the various peptide bonds. In vivo evidence suggests some glucuronidation.

The review made the following recommendations.

A. Recommendation on approvability

This NDA is approvable for the proposed indication.

B. Recommendation for nonclinical studies

No further pharmacology or toxicology studies are needed.

The Pharmacology/Toxicology Supervisor concurred with the reviewer's conclusion that pharmacology and toxicology data support the approval of NDA 22-0201 and that there are no outstanding nonclinical issues related to the approval of degarelix for the proposed indication.

Comment: I concur with the conclusions reached by the pharmacology/toxicology reviewers that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review provided the following executive summary. b(4)

Degarelix is a gonadotropin releasing hormone antagonist. The current submission is the original NDA for degarelix for the treatment of patients with prostate cancer

To support the approval in prostate cancer, the sponsor conducted three phase 2 and one phase 3 study. Patients in the phase 2 studies were randomized to receive various loading doses (40 to 240 mg) followed by various maintenance doses (20 to 160 mg) of degarelix. Testosterone response rate = 0.5 ng/mL was the primary endpoint for all the phase 2 trials. The results from these studies were used to identify a dose which maintained testosterone castration from Day 28 through Day 364 to investigate in phase 3 trials.

In the phase 3 study, patients were randomly assigned to receive degarelix or leuprolide. Two degarelix doses were studied. Both degarelix arms used the 240 mg (40 mg/mL) loading dose and patients received either a 80 mg (20 mg/mL) or 160 mg (40 mg/mL) maintenance dose. Results indicate that the probability of maintaining testosterone levels (T) = 0.5 ng/mL from Day 28 through Day 364 was 97% for the 80 mg maintenance dose group and 98.3% for the 160 mg maintenance dose group (both groups received 240 mg loading doses). In addition, for both degarelix dosing groups, the 95% confidence intervals for the cumulative probability of T = 0.5 ng/mL from Day 28 to Day 364 were > 90% which fits the efficacy criterion pre-specified by the Agency.

Based on the in-vitro studies there are no suspected CYP450 or p-glycoprotein based drug-drug interactions with degarelix. There were no significant degarelix metabolites detected in plasma after subcutaneous administration. There will be no drug-drug interaction information reported in the label.

A study in patients with mild and moderate hepatic impairment was conducted and indicated that patients with hepatic impairment obtained exposures lower than that seen in patients with normal hepatic function. However, this exposure difference was not significant enough to warrant a contraindication or dose modification.

The review made the following recommendation.

> The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-201. This NDA is considered acceptable from a clinical pharmacology perspective.

Comment: I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

A consult was requested from QT Interdisciplinary Review Team. Their overall summary of findings is provided below.

> The two dosing regimens of degarelix, 240 mg at a concentration of 40 mg/ml (240@40) followed by either an 80mg dose at 20 mg/ml concentration (80@20) or 160 mg/ml at a concentration of 40 mg/ml (160@40), prolonged the QT interval with a

similar magnitude and time-course as the active comparator leuprolide 7.5 mg IM every 28 days.

For both degarelix and leuprolide, there was no overt prolongation on day 3. We cannot, however, rule out small effects on the QT interval of <10 ms since the study did not include a positive control. However, the mean change from baseline was approximately 11 ms and 12 ms for degarelix and leuprolide by Day 84 and persisted for the remainder of the study (Day 364).

The time course of QT prolongation is inconsistent with the pharmacokinetics of degarelix. There appears to be a lag time between the time to the maximum concentration of degarelix (Tmax) and QT prolongation. The highest concentration of degarelix is reached in 1 day after the first dose of degarelix (240 mg). No overt QT prolongation was observed on Day 3.

This was an open-label, Phase 3, three-arm, multi-centre stratified, randomized, controlled, parallel-group study to compare the efficacy and safety of degarelix with leuprolide 7.5 mg in patients with prostate cancer. The summary of changes for QTcF results on Day 3 and End of Study is shown in Table 1.

Table 1: Summary of QTCF Findings on Day 1 and End of Study

	Degarelix 240/160 mg	Degarelix 240/80 mg	Degarelix Total	Leuprolide 7.5 mg
Day 3 Corrected QT using Fridericia (msec)				
n	403	407	405	404
Mean baseline	403	407	405	404
Mean change	1.02	3.65	2.36	0.836
Mean % change	0.230%	0.875%	0.559%	0.162%
End of Study Corrected QT using Fridericia (msec)				
n	403	407	405	404
Mean baseline	403	407	405	404
Mean change	10.3	11.7	11.0	13.0
Mean % change	2.54%	2.86%	2.70%	3.17%
Incidence of Markedly Abnormal Changes in ECG Variables				
Corrected QT using Fridericia (msec)	N (n, %)			
>=450	202 (37, 18%)	204 (44, 22%)	406 (81, 20%)	200 (40, 20%)
>=480	202 (7, 3%)	204 (5, 2%)	406 (12, 3%)	200 (7, 4%)
>=500	202 (1, <1%)	204 (2, <1%)	406 (3, <1%)	200 (4, 2%)

Source: Sponsor's Table 10-16 from the CSR for FE200486CS21.

The following are comments from the QT IRT review.

- Although plausible (similar to other androgen inhibitors), we are uncertain about whether the QT prolongation is directly associated with the plasma testosterone level suppression alone and not due the direct effects of degarelix to based on the current observation. Accurate characterization of the relationship between QT prolongation, degarelix concentrations and testosterone inhibition would have required additional ECG observations between Day 3 and Day 84 after degarelix treatment.

• In our opinion, the current QT assessment for degarelix is adequate for the proposed indication of prostate cancer patients who have failed curative therapy and additional characterization of the QT interval is not needed. ——————

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• According to the sponsor, the incidence rate estimates for the degarelix treated patients for cardiovascular and cerebrovascular events were smaller and not significantly different compared to the respective background incidence rates in patients with other GnRH antagonist therapy, derived from the [Surveillance Epidemiology and End Results (SEER)] Medicare linked database. The incidence of cardiovascular (including sudden cardiac death) and cerebrovascular events among men with prostate cancer on GnRH antagonist therapy was higher compared to the background incidence in the target population of prostate cancer patients.

• Similar to the increased risk for other cardiovascular and cerebrovascular events risk versus benefits need to weighed with respect to adverse events related to QT prolongation secondary to degarelix or other androgen inhibitors and feasible risk minimization measures need to be instituted.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The clinical study design and efficacy results are provided in the following excerpt from the agreed-upon package insert.

> The safety and efficacy of degarelix 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 degarelix dosing regimens or leuprolide for one year:
>
> a. degarelix at a starting dose of 240 mg (40 mg/mL) followed by monthly doses of 160 mg (40 mg/mL) subcutaneously,
> b. degarelix 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 days 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 degarelix is effective with respect to achieving and maintaining testosterone suppression to castration levels ($T \leq 50$ ng/dL), during 12 months treatment. The results are shown in Table 2.

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

	DEGARELIX 240/160 mg N=202	DEGARELIX 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 $\leq$ 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)

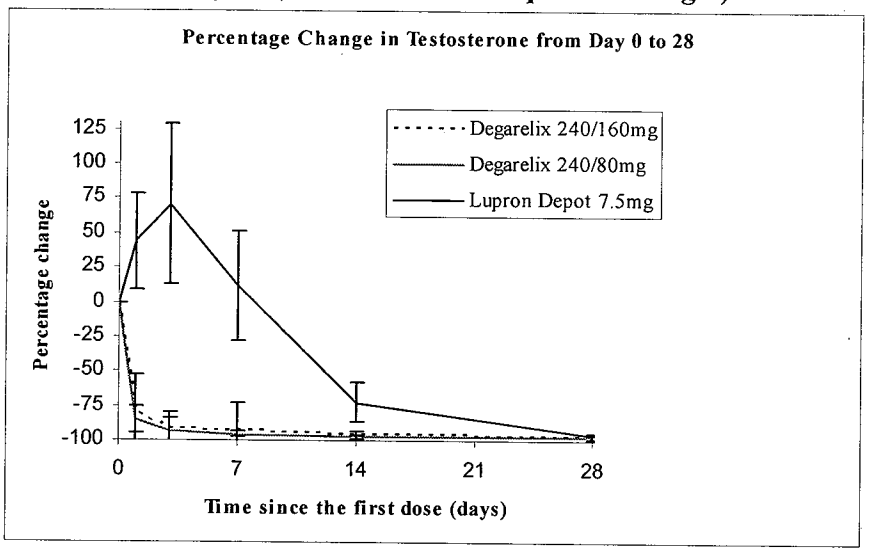

Table 3: Percentage of Patients Attaining Testosterone ≤ 50 ng/dL within the First 28 Days

	Degarelix (240/160 mg) N=202	Degarelix (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 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.

The combined Clinical and Statistical Review made the following recommendation on regulatory action.

This degarelix NDA 22-201, submitted by Ferring Pharmaceuticals, Inc. on February 29th, 2008, requested marketing approval of degarelix, a new gonadotropin releasing

hormone (GnRH) receptor inhibitor, for the treatment of patients with prostate cancer

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The application provided adequate evidence demonstrating that degarelix, administered at the dosing schedule proposed for marketing, is effective in attaining and maintaining biochemical castration levels of testosterone (<0.5 ng/mL) in the studied patient population and has an acceptable safety profile. The reviewers concur with the submitted data and the sponsor's analyses of the data in support of the NDA.

Based on the key findings as discussed below and with the fact that efficacious biochemical castration suppression of testosterone has been recognized and accepted as an established surrogate endpoint for evaluating agents intended to treat prostate cancer through suppressing testosterone, the reviewers recommend regular approval of degarelix at the proposed dosing schedule for the treatment of patients with advance prostate cancer. This also includes patients with advanced symptomatic disease that may be exacerbated by a testosterone surge induced by a GnRH receptor agonist.

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The risk:benefit analysis is provided in the following excerpt.

> The safety and efficacy of degarelix were assessed in an open-label, randomized, multi-center, parallel-group study in patients with prostate cancer. A total of 620 patients were randomized to receive one of the following three treatment regimens for 12 months.
>
> a) Degarelix 240/160 mg: administered subcutaneously at a starting dose of 240 mg, followed by monthly doses of 160 mg initiated after the first month;
> b) Degarelix 240/80 mg: administered subcutaneously at a starting dose of 240 mg, followed by monthly doses of 80 mg initiated after the first month;
> c) Leuprolide 7.5 mg: administered intramuscularly at a does of 7.5 mg monthly initiated at the first day.
>
> Of the patients randomized, 20% had metastatic disease and 80% had non-metastatic disease, including locally advanced disease, localized disease, and PSA relapse only disease after primary definitive therapy. Approximately 81% of patients completed the 12-month treatments.
>
> The primary endpoint was to evaluate the probability of testosterone =0.5 ng/mL from Day 28 to Day 364 in each of the three arms. The results demonstrated that the probabilities of medical castration were 98.3% (95% CI: 94.8% - 99.4%), 97.2%

(93.5% - 98.8%) and 96.4% (92.5% - 98.2%) for the degarelix 240/160 mg, degarelix 240/80 mg and leuprolide 7.5 mg arms, respectively, indicating that degarelix is effective in achieving and maintaining efficacious biochemical castration during 12 months treatment.

The secondary endpoints included comparing changes in serum testosterone within the first month and evaluating proportions of patients achieving medical castration during the period, and assessing changes in other biomarkers including serum luteinizing hormone (LH), follicule-stimulating hormone (FSH), and prostate specific antigen (PSA) during the 12 months. The results showed that no testosterone surges were observed in the degarelix arms and that approximately 96% of patients in the degarelix arms attained medical castration when monitored at 3 days after dosing, compared to none in the leuprolide arm. Nevertheless, almost all the patients in the three arms achieved medical castration by the end of the first month. The changes in LH and FSH were consistent with the mechanism of the study agents and the changes in PSA consistent with the hormone responsiveness of the diseases in the studied patients.

The safety analyses of the study showed that adverse reactions, regardless of causality, were generally comparable between the degarelix arms and leuprolide arm except for injection site reactions and hepatic laboratory abnormalities. The most commonly observed adverse reactions with a frequency of >10% on any either degarelix arm were injection site reactions (e.g. pain, erythema, swelling or induration), hot flushes, weight increases, and increases in transaminases and gamma-glutamyltransferase (GGT).

Injection sites reactions occurred in approximately 40% of patients receiving degarelix compared to less than 1% of patients receiving leuprolide. Between the two degarelix arms, the 240/80 mg arm had 7% less occurrences of the reactions. Hepatic laboratory abnormalities occurred in 10% of patients in the degarelix arms compared to 5% in the leuprolide arm, but with no difference between the two degarelix arms. The abnormalities were generally reversible with the majority as Grade 1/2. Grade 3 hepatic laboratory abnormalities occurred in less than 1% of patients.

Overall, the safety profile appears well acceptable based on the current data. The high incidences of degarelix injection site reactions would not constitute a safety concern.

Relative to the leuprolide, degarelix was associated with 5% greater occurrences of the hepatic laboratory abnormalities. This may be related to degarelix metabolism. Given the majorities of the detected abnormalities were reversible and with the consideration of the known degarelix's pharmacokinetics in patients with hepatic impairment, the differences revealed in this study do not suggest the need of regular monitoring of hepatic function at the proposed degarelix dosing schedule or of a dose modification in patients with hepatic impairment. Other adverse reactions were basically related to the medical castration. Due to the short term of the study by design, the adverse reactions do not reflect long-term safety of medical castration or androgen deprivation.

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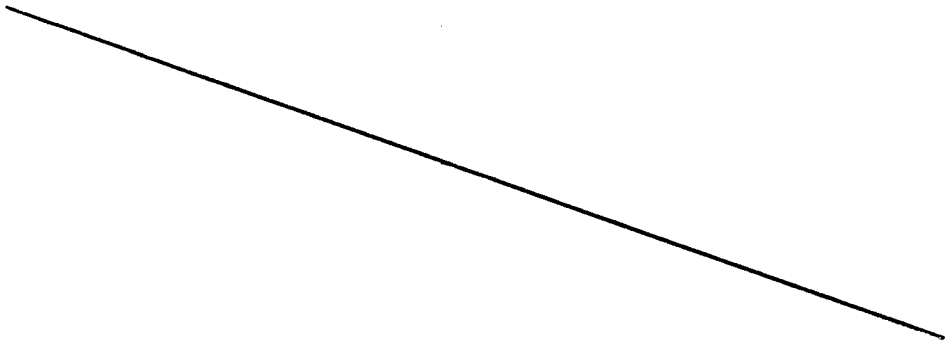
The current safety and efficacy results are adequate to support regular clinical use of degarelix as an androgen deprivation approach for palliative treatment of advanced prostate cancer.



One important feature revealed in the study along with other studies in the NDA is that, unlike a GnRH receptor agonist or activator, degarelix rapidly reduced serum testosterone to the castration levels in approximately 96% patients within a week and with no surges observed, representing an advantage of using a GnRH receptor inhibitor in achieving medical castration. This may be very important in treatment of symptomatic advanced diseases that require an effective urgent medical castration (e.g. newly diagnosed metastasis disease with neurological compromise or with urinary obstructions) in patients who refuse orchiectomy. Currently, there is not a GnRH receptor inhibitor in the market of the States. Clearly, there is a need for this small group of patients.

The review stated that risk evaluation and mitigation strategies are "not indicated with the current analysis results based on the submitted data."

The review provided the following recommendations and justification on post-marketing requirements/phase 4 commitments.

Complete and submit the final study report and datasets for the ongoing extension trial CS21A. The specified dates for the requirement are as follows.

Protocol Submission: 01/2007
Study Start Date: 03/2007
Final Report Submission— 2012

b(4)

This requirement is necessary since long-term safety of degarelix administered in the monthly dosing schedules has not been established. The applicant is currently conducting an extension trial of the key study (CS21) that supports this NDA, Study CS21A. Patients who completed the one-year study of CS21 were eligible to enroll into CS21A. Patients receiving degarelix in CS21 continued monthly maintenance degarelix at the doses (160 mg or 80 mg) as assigned at randomization, and patients

from the leuprolide arm were randomized upon completion of the one-year CS21 study to receive degarelix at either 160 mg or 80 mg monthly. A total of 375 patients were enrolled, with approximately 180 patients in each of the degarelix doses. Of the 375 patients, approximately 65% were from the previous degarelix arms. The study was planned to continue [redacted] With the timelines reported about Study CS21, estimated times of exposure to monthly degarleix treatment for the patients who continued degarelix from CS21 to CS21A would be about [redacted] Therefore, the safety information from CS21A is important to help understand long-term safety profile of degarelix.

b(4)

Comment: I concur with the recommendations of the clinical and statistical reviewers.

8. Safety

The following summary of safety is provided from the agreed-upon package insert.

A total of 1325 patients with prostate cancer received degarelix 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 degarelix 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.

Degarelix was studied in an active-controlled trial (N = 610) in which patients with prostate cancer were randomized to receive degarelix (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

	DEGARELIX 240/160 mg (subcutaneous) N = 202	DEGARELIX 240/80 mg (subcutaneous) N = 207	leuprolide 7.5 mg (intramuscula 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 DEGARELIX 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 DEGARELIX for 1 year. There is no indication that the efficacy or safety of DEGARELIX treatment is affected by antibody formation.

Comment: Because the safety profile of long-term administration has not been determined and because of liver enzyme elevations in 10% of patients, a post-marketing trial requirement is indicated as described below.

9. Advisory Committee Meeting

This application was not referred to the Oncologic Drugs Advisory Committee for review because the key study used an established surrogate endpoint, and the results of the study did not raise significant issues with respect to the efficacy and safety of degarelix in the intended population.

10. Pediatrics

Since prostate cancer does not occur in the pediatric population a pediatric waiver is appropriate.

11. Other Relevant Regulatory Issues

The DSI overall assessment of findings and recommendations stated the following.

The inspection for this NDA consisted of one US and 2 foreign (Romania) clinical sites, as well as the Sponsor. Observations noted above are based on the Form FDA 483, preliminary results, EIRs and communications from field investigators. The final inspection reports for Sites ———— are pending. In general, based on the inspection of the 3 clinical study sites combined with the sponsor/monitor audit for this NDA, the inspectional findings with the isolated deficiencies noted with the sponsor/monitor audit, support validity of data as reported by the sponsor under this NDA. b7

Upon receipt and review of the final inspection reports, an inspection summary addendum will be generated if additional observations of clinical or regulatory significance are discovered.

Financial disclosure is discussed on page 15 of the medical review.

Disclosure of financial interests of the investigators who conducted the clinical studies supporting this NDA was submitted in the FDA form 3455. The disclosure was certified by Ronald T. Hargreaves, Ph.D, Vice President of Regulatory Affairs for the applicant. All of the investigators disclosed no financial conflict of interest, either a proprietary interest or a significant equity in the applicant.

The key study that supports the efficacy and safety labeling claims involved 80 study centers in 11 countries, with centralized laboratory analyses of serum testosterone and other surrogate markers important for understanding how degarelix works. This study design and conduct would minimize the effect of financial conflicts, if any, on the outcome of the study.

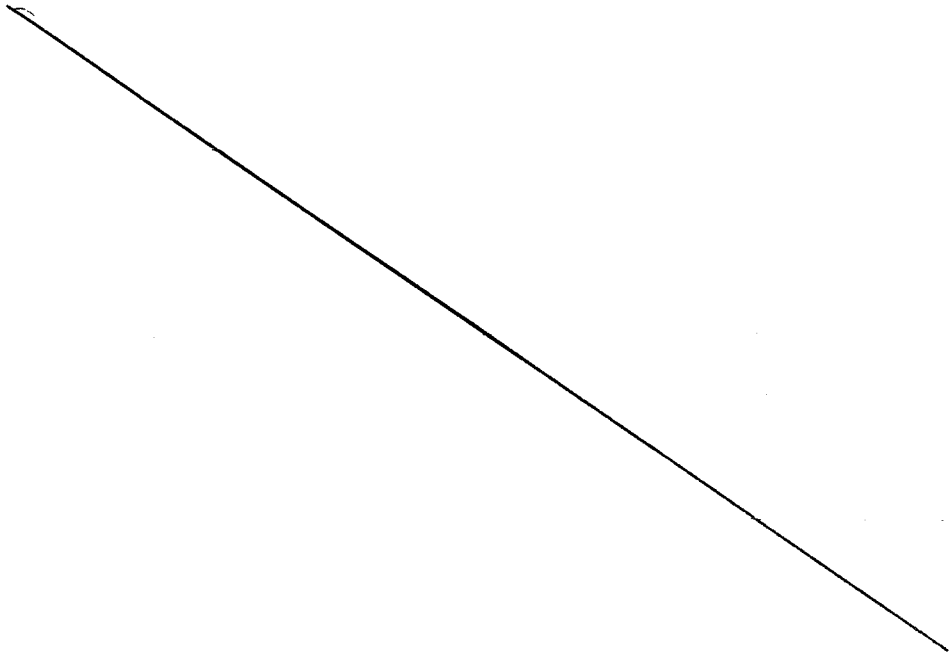
Comment: There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name

The DMEPA proprietary name review states the following.

> During the initial steps on the trade name review process, the Division of Drug Marketing, Advertising, and Communications (DDMAC) did not recommend the use of the proposed trade name, Firmagon,



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An alternative tradename is under review by DMEPA but the review will not be completed by the action date.

- Physician labeling: Agreement has been reached on the physician labeling.

- Carton and immediate container labels: Agreement has been reached on carton and container labels.

- Patient labeling/Medication guide: The applicant submitted a Patient Package Insert. The DRISK review of 12/20/08 recommended a number of revisions which have been accepted by the applicant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The risk:benefit assessment is acceptable. Degarelix rapidly lowers testosterone levels to castrate levels without the transient surge that is seen with GnRH agonists. Except for reversible injection site reactions and LFT elevations, the safety profile of degaralix is similar to the GnRH agonists. Abarelix, the only currently approved GnRH antagonist, was approved with restricted distribution because of immediate-onset systemic allergic reactions, including hypotension and syncope. These reactions were not seen with degaralix.

- Recommendation for Postmarketing Risk Management Activities

  Routine postmarketing surveillance

- Recommendation for other Postmarketing Study Requirements/Commitments

  Because the safety profile of long-term administration has not been determined and because of liver enzyme elevations in 10% of patients, the following postmarketing trial requirement is recommended.

  Complete the ongoing extension trial CS21A and submit annual reports and a final study report with datasets. The specified dates for the requirement are as follows.

Protocol Submission:	January 2007
Study Start Date:	March 2007
First Annual Report Submission:	March 2009
Second Annual Report Submission:	March 2010
Third Annual Report Submission:	March 2011
Final Report and Dataset Submission:	——— 2012

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/s/

Robert Justice
12/24/2008 02:24:59 PM
MEDICAL OFFICER