

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-201

OFFICE DIRECTOR MEMO

Office Director Memo

Date	December 22, 2008
From	Richard Pazdur, MD
Subject	Office Director Summary
NDA/BLA #	22-201
Supplement #	
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:	<i>Approval</i>

Material Reviewed/Consulted	
OND Action Package, including:	
Medical Officer Review	X (including Division Director)
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

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Summary:

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 a GnRH receptor antagonist.

A total of 620 patients were randomized to receive one of two degarelix dosing regimens or leuprolide for one year: degarelix at a starting dose of 240 mg followed by monthly doses of 160 mg subcutaneously, degarelix at a starting dose of 240 mg followed by monthly doses of 80 mg subcutaneously, or leuprolide 7.5 mg intramuscularly monthly. The primary objective was to demonstrate that degarelix is effective in achieving and maintaining testosterone suppression to castration levels (≤ 50 ng/dL) during 12 months treatment. The medical castration rates were 98.3% (95% CI: 94.8%; 99.4%) in the degarelix 240/160 mg arm, 97.2% (95% CI: 93.5%; 98.8%) in degarelix 240/80 mg arm, and 96.4% (95% CI: 92.5%; 98.2%) in the leuprolide 7.5 mg arm. The key secondary analyses showed that no testosterone surges were observed in the degarelix arms and that 96% of patients attained medical castration 3 days after the first degarelix dose compared to no patients receiving leuprolide.

Table 1: Medical Castration Rates (Testosterone ≤ 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

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Table 2: Percentage of Patients Attaining Testosterone \leq 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%

The most commonly observed adverse reactions (frequency of \geq 10%) in either degarelix arm included injection site reactions (e.g., pain, erythema, swelling or induration), hot flashes, weight increase, and increases in transaminases and gamma-glutamyltransferase. The majority of the adverse reactions were grade 1/2 in severity and grade 3/4 adverse reactions were uncommon. The injection site reactions were transient, with frequencies of 35-44% in the degarelix arms compared to a frequency of <1% in the leuprolide arm. Hepatic laboratory abnormalities were generally reversible, with grade 3 abnormalities in less than 1% of patients. There were no important differences in adverse reactions between the two degarelix arms, except for fewer injection site reactions in the 240/80 mg arm.

The recommended dosing regimen is a starting dose of 240 mg given as two subcutaneous injections of 120 mg each followed by monthly maintenance doses of 80 mg given as a single subcutaneous injection.

Please refer to Dr. Justice's review for a discussion of the chemistry and manufacturing review, nonclinical pharmacology/toxicology review, clinical pharmacology/biopharmaceutics review.

Clinical and Statistical Review (details)

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 advanced 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, multicenter, 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 dose 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 \leq 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), follicle-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.

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.

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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

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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 until patient withdrawal, sponsor discontinuation of the development, or the time degarelix becomes commercially available. With the

timelines reported about Study CS21, estimated times of exposure to monthly degarelix treatment for the patients who continued degarelix from CS21 to CS21A would be about 2-3 years. Therefore, the safety information from CS21A is important to help understand long-term safety profile of degarelix.

Regulatory Decision: Approval

The risk:benefit assessment is acceptable. Degarelix rapidly lowers testosterone levels to castrate levels without the transient surge which is seen with GnRH agonists. Except for reversible injection site reactions and LFT elevations, the safety profile of degarelix is similar to GnRH agonists. Abarelix, the only other 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 degarelix.

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Richard Pazdur
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