CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-201

CHEMISTRY REVIEW(S)

NDA 22201

degarelix for Injection

Ferring Pharmaceuticals, Inc.

Debasis Ghosh, M. Pharm., Ph.D.

Office of New Drug Quality Assessment
Pre-Marketing Assessment and Manufacturing
Science Division III, Branch V

Table of Contents

1. NDA 22-201

2. REVIEW #: 2

3. REVIEW COMPLETED ON: Dec 24, 2008

4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA - CMC	2/29/2008
Amendment 0004	9/30/2008
Amendment 0006	11/12/2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Labels submitted on Dec 22, 2008	N/A
Labels submitted on Dec 23, 2008	N/A

7. NAME & ADDRESS OF APPLICANT:

Name: Ferring Pharmaceuticals, Inc

Address: 4 Gatehall Drive, Third Floor, Parsipanny, NJ 07054

Representative: Ronald T. Hargreaves, Ph.D.

Telephone: 973-796-1620

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	degarelix for injection
c) Code Name/# (ONDQAC only):	FE 200486 or PPL-101

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: GnRH receptor blocker

11. DOSAGE FORM: Sterile powder for injection

12. STRENGTH/POTENCY: 80 mg and 120 mg of degarelix

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: _x__Rx ___OTC

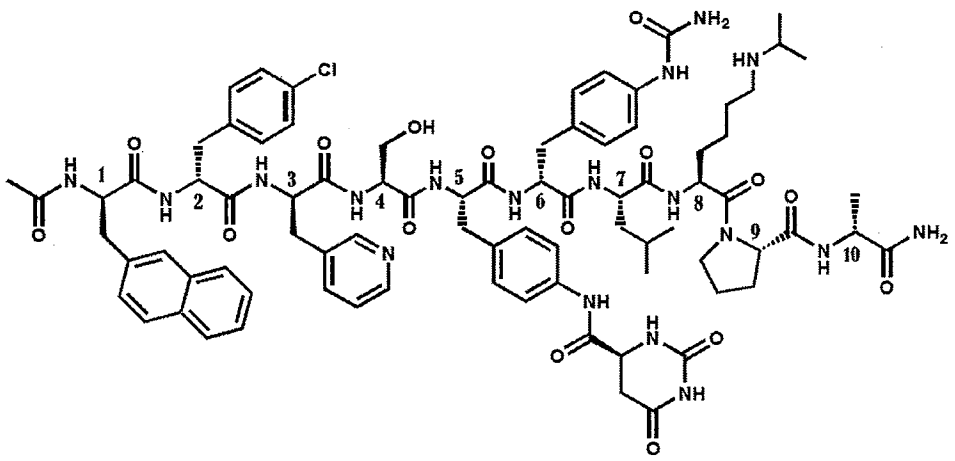
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-Dalanyl-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-

Appears This Way
On Original



The empirical formula is: $C_{82}H_{103}N_{18}O_{16}Cl$
The molecular weight is 1630.75 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	III		—	4	N/A	N/A	None
—	III			1	Adequate	28-Oct-2008	None

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51222	This is applicant's IND for the drug product

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
DMEPA	Pending		
EES	OC Recommendation	Dec 19, 2008	
Pharm/Tox	N/A		William D. McGuinn, Ph.D.
Biopharm	N/A		Julia Bullock, Ph.D.
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion	Nov 25, 2008	Debasis Ghosh, Ph.D.
Microbiology	Satisfactory	Dec 2008	John Metcalfe, Ph.D.

The Executive Summary

I. 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.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product
degarelix drug product is a lyophilized powder (80 mg or 120 mg) packaged in a glass vial ——— b(4)
——— equipped with 20 mm ——— rubber-type stopper ———
——— and flip-off seal.

———————————————— b(4)

The lyophilized powder should be reconstituted with sterile Water for Injection, USP (WFI) before subcutaneous administration. After reconstitution, the concentration of degarelix in 120 mg and 80 mg of reconstituted solution of drug product would be 40 mg/mL and 20 mg/mL, respectively.

Note 2: Following a teleconference with FDA on Nov 12, 2008, the applicant agreed ——— b(4)
———

Degarelix drug product contains degarelix acetate and mannitol. Degarelix exists as acetate in the lyophilized powder form. The exact ratio of degarelix to acetate varies within the range of established acceptable limits. The amount of degarelix in the vial corresponds to the free base, degarelix, only. Mannitol is used as an excipient. It is highly soluble in water and widely used in parenteral formulations ——— of the parenteral product. Amount of mannitol present in both 120 mg and 80 mg b(4)
degarelix drug product are different because of different dilution of drug product during reconstitution. It is adjusted to maintain the level of 5% of mannitol in the reconstituted solution ———
——— of the formulation for parenteral administration.

Lyophilized degarelix drug product is soluble in water for injection USP. However, on standing at ambient temperature, the solution may start forming a non-resuspendable turbid solution after more than 4 hours and finally it forms a viscous gel. Based on analytical studies, the reconstituted solution should be used within an hour of reconstitution at ambient temperature. [redacted] b(4)

[redacted] It is important to remember that degarelix solution should be discarded if the solution becomes turbid indicating self-aggregation.

[redacted] b(4)

b(4)

Based on the available drug product stability data presented in the original submission (Serial No. 0000), the drug powder (120 mg) containing degarelix acetate and mannitol was found to be stable during long-term storage (25 °C/60% RH) for 24 months. Hence, the drug product is recommended to be labeled for 24-month expiry date.

The decision to extend the expiry date depends on various factors including the availability of additional stability data and justification for the extension. The label for the reconstituted solution should indicate the use of the product within one hour of reconstitution.

Drug substance

Drug substance, degarelix, is a linear decapeptide containing seven unnatural amino acids and eleven chiral centers. It is highly soluble in water [redacted] It is a white to b(4)
off-white amorphous powder [redacted] It has a tendency to self-aggregate [redacted] and forms a turbid mixture from solution [redacted] UV spectra of degarelix showed three absorption maxima at 202, 226 and 245 nm. It is found to be photostable when subjected to ICH photostability studies.

[redacted] b(4)

b(4)

A ~ month re-test period when stored at 5 °C ± 3 °C appears to be acceptable.

b(4)

B. Description of How the Drug Product is Intended to be Used

degarelix for solution is indicated for the treatment of patients with advanced prostate cancer. Subcutaneous administration of degarelix immediately forms a depot at the site of injection and the drug is intended to be released from the depot for extended time. The applicant submitted NDA application for two different strengths of degarelix. The starting dose of 240 mg (120 mg/3mL x 2) followed by a maintenance dose of 80 mg (80 mg/4 mL) for a total of one-month dosing regimen.

Prior to administration, degarelix powder must be reconstituted with water for injections. For starting dose, two degarelix drug product 120 mg should be used. Each 120 mg drug product should be reconstituted with 3 mL of water for injections and should be administered subcutaneously at two different sites. For maintenance dose, 80 mg drug product should be reconstituted with 4.2 mL water for injections. The reconstituted solution should be used within one hour from the initiation of the reconstitution process. Since reconstitution time is about 15 min, the proper instruction should be provided to ensure the administration of the product within approximately 45 minutes after reconstitution. The reconstituted solution should be administered as subcutaneous injection in the abdominal region. 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. Injection site should vary periodically. It is not to be administered intravenously.

C. Basis for Approvability or Not-Approval Recommendation

The applicant provided adequate CMC related information to establish the identity, integrity, strength and purity of the drug product. The degarelix for injection is recommended for an approvable action by ONDQA for manufacturing and controls under Section 505 of the Act.

III. Administrative

A. Reviewer's Signature

Debasis Ghosh, M. Pharm., Ph.D.

B. Endorsement Block

ChemistName/Date:	Debasis Ghosh, Ph.D./Dec 23, 2008
Chemistry, Division Director/Name/Date	Rik Lostritto, Ph.D./Dec 23, 2008

C. CC Block:

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Debasis Ghosh
12/24/2008 12:49:53 PM
CHEMIST

Richard Lostritto
12/24/2008 12:55:21 PM
CHEMIST

ONDQA Division Director's Memo
NDA 22-201, Degarelix 80 mg and 240 mg powder for injection
(for subcutaneous injection only)
Date: 23-DEC-2008

Introduction

Degarelix 80 mg and 240 mg powder for injection is indicated for use in advanced prostate cancer. Degarelix is provided as a sterile lyophilized powder, packaged in glass vials. There are two strength presentations. These are 80 mg/vial (one vial per carton), and 240 mg (starting dose) packaged as two vials each containing 120mg per vial (2 per box). The lyophilized powder is to be reconstituted only with WFI (NOT bacteriostatic WFI) and administered subcutaneously only.

Adminstrative

The original submission of this 505(b)(1) NDA was received 29-FEB-2008 from Ferring Pharmaceuticals, Inc. Several amendments to the NDA were received and reviewed between 30-SEP-2008 and today and were either responses to CMC deficiencies or labeling deficiencies which required ONDQA review input. The associated IND is 51,222.

As of this writing and acceptable proprietary name has not been provided "FIRMAGON"was rejected by DMEPA. As of this writing, no proprietary name has been accepted by the Agency.

There are no outstanding CMC deficiencies or agreements. On 22-DEC-2008, an overall satisfactory report appeared in the EES file for this drug product.

A recommendation for approval (AP) from ONDQA is recommended.

Drug Substance

Degarelix ($C_{82}H_{103}N_{18}O_{16}Cl$, MW=1630.75), is a linear decapeptide containing seven non-natural amino acids and it has eleven chiral centers. It is highly water soluble. Degarelix is prepared by [redacted] Variable amounts of [redacted] the drug substance's bulk mass. The drug substance appears to be [redacted] It has a retest period of [redacted] months when stored at 5C. b(4)

Drug Product (Degarelix)

The drug product is a sterile lyophilized powder of degarelix acetate (variable percentage from the drug substance) and mannitol. The amount of mannitol varies between the two strengths to give a resultant concentration of 5% mannitol in the reconstituted solution for subcutaneous injection. b(4)

The 80 mg strength (one vial) is reconstituted with [redacted] mL of WFI and the 240 mg strength (as 2 vials of 120 mg each) is reconstituted with 6 mL of WFI (as 3 mL per vial; 2 vials). b(4)

The reconstituted solution self-associates and forms a viscous gel in the subcutaneous tissue a few minutes after administration. This will also occur in vivo, so the reconstituted drug product has an in-use life of one hour from initiation of the reconstitution process.. Reconstitution can take as long as 15 minutes; leaving a 45 minute window for actual administration to the patient. NOTE that bacteriostatic water for injection is ***not*** to be used for reconstitution because it forms a precipitate.

[redacted] b(4)

The approved drug product shelf life is 24 months

Rik Lostritto, Ph.D., Director, ONDQA Division III

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/s/

Richard Lostritto
12/24/2008 12:02:01 PM
CHEMIST

NDA 22201

degarelix for Injection

Ferring Pharmaceuticals, Inc.

Debasis Ghosh, M. Pharm., Ph.D.

Office of New Drug Quality Assessment
Pre-Marketing Assessment and Manufacturing
Science Division III, Branch V

Table of Contents

Chemistry Review Data Sheet

1. NDA 22,201

2. REVIEW #: 1

3. REVIEW COMPLETED ON: Dec 23, 2008

4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA - CMC	2/29/2008
Amendment 0004	9/30/2008
Amendment 0006	11/12/2008

7. NAME & ADDRESS OF APPLICANT:

Name: Ferring Pharmaceuticals, Inc

Address: 4 Gatehall Drive, Third Floor, Parsipanny, NJ 07054

Representative: Ronald T. Hargreaves, Ph.D.

Telephone: 973-796-1620

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	N/A
b) Non-Proprietary Name (USAN):	degarelix for injection
c) Code Name/# (ONDQAC only):	FE 200486 or PPL-101

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: GnRH receptor blocker

11. DOSAGE FORM: Sterile powder for injection

12. STRENGTH/POTENCY: 80 mg and 120 mg of degarelix

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: _x__Rx ___OTC

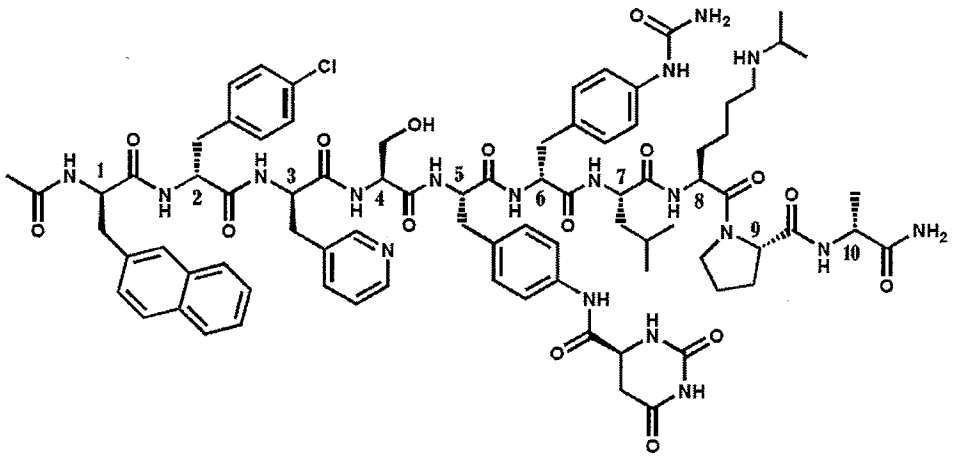
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-Dalanyl-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-

Chemistry Review Data Sheet



The empirical formula is: $C_{82}H_{103}N_{18}O_{16}Cl$
The molecular weight is 1630.75 Da

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	4	N/A	N/A	None
[redacted]	III	[redacted]	[redacted]	1	Adequate	28-Oct-2008	None

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
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6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	51222	This is applicant's IND for the drug product

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
DMEPA	Pending		
EES	OC Recommendation	Dec 19, 2008	
Pharm/Tox	N/A		William D. McGuinn, Ph.D.
Biopharm	N/A		Julia Bullock, Ph.D.
LNC	N/A		
Methods Validation	N/A		
OPDRA	N/A		
EA	Categorical Exclusion	Nov 25, 2008	Debasis Ghosh, Ph.D.
Microbiology	Satisfactory	Dec 2008	John Metcalfe, Ph.D.

Chemistry Review for NDA 22201

The Executive Summary

I. 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 pending satisfactory resolution of labeling issues.

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

Not applicable.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product

degarelix drug product is a lyophilized powder (80 mg or 120 mg) packaged in a glass vial [redacted] equipped with 20 mm [redacted] rubber-type stopper [redacted] and flip-off seal. b(4)

[redacted] b(4)

lyophilized powder should be reconstituted with sterile Water for Injection, USP (WFI) before subcutaneous administration. After reconstitution, the concentration of degarelix in 120 mg and 80 mg of reconstituted solution of drug product would be 40 mg/mL and 20 mg/mL, respectively.

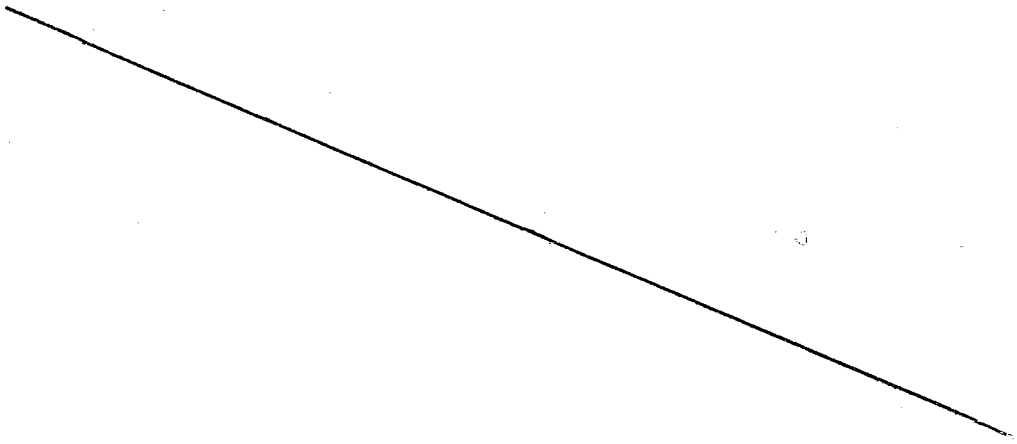
Note 2: Following a teleconference with FDA on Nov 12, 2008, the applicant agreed to [redacted] b(4)

Degarelix drug product contains degarelix acetate and mannitol. Degarelix exists as acetate in the lyophilized powder form. The exact ratio of degarelix to acetate varies within the range of established acceptable limits. The amount of degarelix in the vial corresponds to the free base, degarelix, only. Mannitol is used as an excipient. It is highly soluble in water

and widely used in parenteral formulations _____ of the parenteral product. Amount of mannitol present in both 120 mg and 80 mg degarelix drug product are different because of different dilution of drug product during reconstitution. It is adjusted to maintain the level of 5% of mannitol in the reconstituted solution _____ _____of the formulation for parenteral administration. b(4)

Lyophilized degarelix drug product is soluble in water for injection USP. However, on standing at ambient temperature, the solution may start forming a non-resuspendable turbid solution after more than 4 hours and finally it forms a viscous gel. Based on analytical studies, the reconstituted solution should be used within an hour of reconstitution at ambient temperature. _____ b(4)

_____. It is important to remember that degarelix solution should be discarded if the solution becomes turbid indicating self-aggregation.



b(4)

Based on the available drug product stability data presented in the original submission (Serial No. 0000), the drug powder (120 mg) containing degarelix acetate and mannitol was found to be stable during long-term storage (25 °C/60% RH) for 24 months. Hence, the drug product is recommended to be labeled for 24-month expiry date.

The decision to extend the expiry date depends on various factors including the availability of additional stability data and justification for the extension. The label for the reconstituted solution should indicate the use of the product within one hour of reconstitution.

Drug substance

Drug substance, degarelix, is a linear decapeptide containing seven unnatural amino acids and eleven chiral centers. It is highly soluble in water _____ b(4)
_____ It is a white to off-white amorphous powder and _____

[redacted]. It has a tendency to self-aggregate by [redacted] and forms a turbid mixture from solution. [redacted]. UV spectra of degarelix showed three absorption maxima at 202, 226 and 245 nm. It is found to be photostable when subjected to ICH photostability studies. b(4)

[redacted] b(4)

[redacted] b(4)

A [redacted]-month re-test period when stored at 5 °C ± 3 °C appears to be acceptable. b(4)

B. Description of How the Drug Product is Intended to be Used

degarelix for solution is indicated for the treatment of patients with advanced prostate cancer. Subcutaneous administration of degarelix immediately forms a depot at the site of injection and the drug is intended to be released from the depot for extended time. The applicant submitted NDA application for two different strengths of degarelix. The starting dose of 240 mg (120 mg/3mL x 2) followed by a maintenance dose of 80 mg (80 mg/4 mL) for a total of one-month dosing regimen.

Prior to administration, degarelix powder must be reconstituted with water for injections. For starting dose, two degarelix drug product 120 mg should be used. Each 120 mg drug product should be reconstituted with 3 mL of water for injections and should be administered subcutaneously at two different sites. For maintenance dose, 80 mg drug product should be reconstituted with 4.2 mL water for injections. The reconstituted solution should be used within one hour from the initiation of the reconstitution process. Since reconstitution time is about 15 min, the proper instruction should be provided to ensure the administration of the product within approximately 45 minutes after reconstitution. The reconstituted solution should be administered as subcutaneous injection in the abdominal region. 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. Injection site should vary periodically. It is not to be administered intravenously.

C. Basis for Approvability or Not-Approval Recommendation

The applicant provided adequate CMC related information to establish the identity, integrity, strength and purity of the drug product. The degarelix for injection is recommended for an approvable action by ONDQA for manufacturing and controls under Section 505 of the Act pending satisfactory resolution of labeling issues.

III. Administrative

A. Reviewer's Signature

Debasis Ghosh, M. Pharm., Ph.D.

B. Endorsement Block

ChemistName/Date:	Debasis Ghosh, Ph.D./Dec 23, 2008
Chemistry, Division Director/Name/Date	Rik Lostritto, Ph.D./Dec 23, 2008

C. CC Block:

157 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-2

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/s/

Debasis Ghosh
12/23/2008 10:56:30 AM
CHEMIST

Richard Lostritto
12/24/2008 11:18:44 AM
CHEMIST

Initial Quality Assessment
Branch V
Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division:	Division of Drug Oncology Products
NDA:	22-201
Applicant:	Ferring Pharmaceuticals, Inc.
Stamp date:	28-FEB-2008
PDUFA Date:	28-DEC-2008 (standard review anticipated)
Proposed Trade Name:	Firmagon
Established Name:	Degarelix
Laboratory Code:	Not applicable
Dosage Form:	Powder [redacted] for injectable [redacted] b(4)
	80 and 120 mg/vial
Route of Administration:	Injectable
Regulatory Filing Category:	505(b)(1), Type 1/NME
Indication:	Treatment of advanced prostate cancer

Pharmaceutical Assessment Lead: Sarah C. Pope, Ph.D.

	YES	NO
ONDQA Fileability:	√	___
Draft Comments for 74-Day Letter:	√	___

Summary, Critical Issues and Comments

A. Summaries

Background Summary

NDA 22-201 is submitted for Firmagon (degarelix for injection, 80 mg/vial and 120 mg/vial), intended for treatment of advanced prostate cancer. Degarelix is a new molecular entity and is submitted for review pursuant to Section 505(b)(1) of the Food, Drug and Cosmetic Act. Reference is made to one active Investigational New Drug application, IND 51,222, for the documented drug development history.

Related development meetings were conducted periodically throughout the development program. CMC comments were issued in the Applicant's 17-OCT-2007 preNDA meeting. Additional CMC-specific comments were conveyed on 02-NOV-2004 in response to the Applicant's EOP2 CMC meeting request; the EOP2 CMC meeting was subsequently canceled. A preIND meeting was held on 12-MAR-2001.

Drug Substance Summary

Degarelix is a New Molecular Entity. It is a linear decapeptide (Figure 1) which is manufactured as its acetate salt. Degarelix contains ten chiral centers in its backbone, and five of the amino acids are in the D configuration. The amino acid residue at position five possesses its own chiral center in the side-chain, which results in a total of eleven chiral centers for the overall drug substance. b(4)

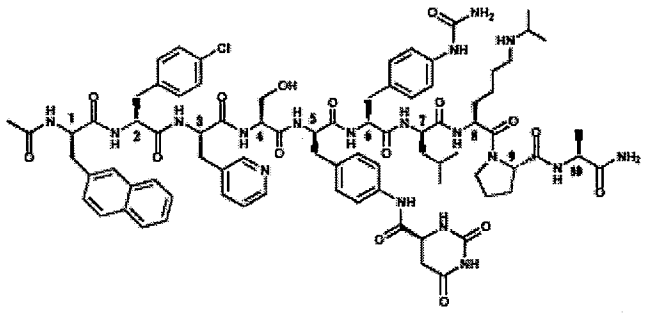

Figure 1. Degarelix (Relative MW=1630.8 Da)

b(4)

Degarelix has been accepted as a United States Adopted Name (USAN). Additional terminology may reference the Applicant's laboratory codes "FE 200486" and "PPL 101". The CAS number for degarelix is 214766-78-6.

Once synthesized, degarelix (acetate) is tested for conformance to specifications for the following attributes: description, identification [redacted] b(4) The Applicant also includes specifications for any unspecified impurity, any unspecified degarelix-related impurity, and sum of impurities. Since the dosage form is an injectable suspension, the particle size distribution and specific surface area of the drug substance may be critical to the performance of this product.

The Applicant provides primary stability data for five production scale batches. Stability testing was conducted under long term (5°C±3°C) and accelerated (25°C/60%RH) conditions. The NDA submission includes 36 months of long term data for two batches, along with 24 months of long term data for the remaining three batches. Forced degradation testing was also conducted on a primary stability batch.

The Applicant is proposing a retest period of [redacted] months for storage conditions of 5°C±3°C. b(4)

Drug Product Summary

The drug product is formulated with mannitol as a [redacted] product for reconstitution with WFI, prior to subcutaneous injection. Once reconstituted, the resulting solution has a concentration of [redacted] The extractable dose of suspension is either 80 or 120 mg, depending on which of the dosage strengths is used. According to USP, the proposed term for the dosage form is "powder [redacted] for injectable [redacted] b(4)

[redacted] The active vials do not include any additional excipients other than mannitol. The 120-mg dosage strength is intended to be a loading dose of degarelix, while the 80-mg dosage strength is intended to be a maintenance dose. b(4)

[redacted] b(4)

Degarelix is packaged into a glass vial which is stoppered with a [redacted] rubber closure and then sealed with a flip-off seal. [redacted]

[redacted] b(4)

The Applicant proposes a reduced stability test design, based on ICH Q1D, for the three primary stability batches. The provided data cover six months of accelerated testing (40°C/75% RH) and

b(4)

18 months of long term testing (25°C/60% RH). The Applicant provides statistical analyses for — specified impurities as well as total degradation products.

The Applicant proposes a ——— expiration dating period for the drug product, presumably when stored at room temperature. b(4)

B. Critical issues for review and recommendation

Drug Substance

a. [redacted] b(4)

b. The Applicant specifies each of the following as intermediates in the synthesis of degarelix:

[redacted] b(4)

——— The adequacy of the proposed in-process and release specifications should be confirmed relative to each intermediate.

c. There appears to be a discrepancy between the number of intermediates stated by the Applicant ——— with the information provided in the manufacturing section ——— This should be clarified in the CMC review. b(4)

d. [redacted] b(4)

e. [redacted] b(4)

f. Since the dosage form is an injectable ——— the particle size distribution and specific surface area of the drug substance may be critical to the performance of this product. These attributes should be carefully assessed during the review of the drug substance specifications. b(4)

Drug Product

a. The proposed manufacturing process is conventional for injectable formulations, and compendial excipients are stated in the drug product composition. While the submitted manufacturing and compositional information should be completely assessed, there are no significant (high-risk) triggers in the provided process and compositional information.

b. A test for resuspendability is not included in the proposed drug product specifications. The omission of this attribute should be carefully evaluated.

c. The Applicant proposes a stability matrixing scheme based on ICH Q1D. The adequacy of this scheme should be carefully assessed while simultaneously determining the adequacy of the provided statistical analyses for support of the matrix and proposed expiration dating period.

d. [redacted] b(4)

e. Due to the injectable nature of the formulation, all drug product manufacturing and controls information should also be consulted to the Office of Microbiology for review.

f. The Applicant intends to market two dosage strengths of the product. While the comparative formulations are linear in composition, the comparative performance(s) should be analyzed during the review cycle. Any noted differences between the two dosage strengths should be evaluated and discussed internally for potential impact of clinical performance.

g. The Applicant does not provide Letters of Authorization for any of the packaging components. While the information provided in the NDA may well be adequate to support the use of these components, this should be confirmed during the CMC review.

D. Comments for 74-day Letter:
None.

E. Recommendation for fileability: **Fileable**

Fileability Template

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	√		
5	Is a statement provided that all facilities are ready for GMP inspection?	√		Comment issued in 17-OCT-2007 preNDA meeting
6	Has an environmental assessment report or categorical exclusion been provided?	√		An environmental assessment report is included. This may need a consult as necessary.
7	Does the section contain controls for the drug substance?	√		
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has a section been provided on pharmaceutical development/ investigational formulations section?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?	√		
16	Have all consults been identified and initiated? (bolded items to be handled by ONDQA PM)		√ √ √ √ √ √	**Microbiology** Pharm/Tox (NME) Biopharm Statistics OCP/CDRH/CBER LNC DMETS/ODS **EER**

Have all DMF References been identified? Yes ( ) No (√)

DMF Number	Holder	Description	LOA Included
None			

Recommendation for Team Review:

This NDA includes a significant portion of drug substance manufacturing information. However, the drug product information is conventional in nature, and the CMC review will be conducted in conjunction with a microbiological assessment/review. The majority of the critical quality attributes for the drug product are microbiological (sterility, endotoxin limits, etc.), and the CMC review for the drug product should be straightforward.

The team review approach is not recommended for this NDA.

Sarah C. Pope, Ph.D. Pharmaceutical Assessment Lead	20-Mar-2008 Date
Ravi Harapanhalli, Ph.D. Branch Chief	20-Mar-2008 Date

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/s/

Sarah Pope
3/20/2008 04:26:31 PM
CHEMIST

Ravi Harapanhalli
4/1/2008 12:19:40 PM
CHEMIST