CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-484

Chemistry Review(s)

CHEMISTRY REVIEW

NDA 21-484

Bravelle (urofollitropin for injection, purified)

Ferring Pharmaceuticals, Inc.

Martin Haber, Ph.D.
Division of Metabolic and Endocrine Drugs

Table of Contents

Chemistry Review Data Sheet

1. NDA # 21-484

2. REVIEW #: 1

3. REVIEW DATE: October 31, 2002

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

None

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	2/15/02

7. NAME & ADDRESS OF APPLICANT:

Name:	Ferring Pharmaceuticals, Inc.
Address:	120 White Plains Road, Suite 400
Representative:	Dr. Ronald V. Nardi
Telephone:	(914) 333-8900

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Bravelle

b) Non-Proprietary Name (USAN): Urofollitropin, purified
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type:
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Infertility

11. DOSAGE FORM: Lyophilized powder for Injection

12. STRENGTH/POTENCY: 75 IU

13. ROUTE OF ADMINISTRATION: Subcutaneous and Intramuscular Injection

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

___x__SPOTS product – Form Completed

_____Not a SPOTS product

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

Follicle Stimulating Hormone (FSH), a glycoprotein hormone containing two peptide subunits of about [redacted] (including carbohydrate). The alpha subunit contains 92 amino acids of which two have attached carbohydrates and the beta subunit contains 111 amino acids of which

two have attached carbohydrates. The hormone is purified from the urine of postmenopausal women. See Chemistry Review #1 of NDA 21-289 for amino acid sequences.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			3	Adequate	3/3/94	Dr. Niu reviewed for viral clearance and no changes were made to those steps, ANDAs
	III			3	Adequate	3/14/00	Dr. Tran, NDA 18261
	III			3	Adequate	10/22/99	Dr. Harapanhalli, NDA 21092
	III			3	Adequate	1/4/01	Dr. Powers, ANDA

[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
Repronex (menotropins) NDA	NDA 21-047	Ferring Pharmaceuticals
Urofollitropin, purified	IND	Ferring Pharmaceuticals
Bravelle (urofollitropin, purified)	NDA 21-289	Ferring Pharmaceuticals

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Satisfactory	10/8/02	
Pharm/Tox	NA		
Biopharm	NA		
LNC	NA		
Methods Validation	NA		
OPDRA	NA		
EA	NA		
Microbiology	NA		

APPEARS THIS WAY ON ORIGINAL

The Chemistry Review for NDA 21-289

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval

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

In their 4/18/02 Amendment to NDA 21-289, Ferring has agreed to make developing and implementing identification tests for lactose and polysorbate 20 (for drug product release) a Phase IV commitment to be completed within one year of NDA approval.

II. Summary of Chemistry Assessments

Background: This administrative NDA cross-references all CMC information to the approved NDA 21-289, Bravelle, which contains the exact same drug. Therefore, no chemistry review is required.

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

The drug product is a sterile lyophilized powder containing [redacted] purified urofollitropin (follicle stimulating hormone or FSH), 23 mg of lactose, 5 µg of polysorbate 20 and small amounts of sodium phosphate buffer in a glass vial with rubber stopper. The product contains 82.5 IU of FSH/vial and is labeled to deliver 75 IU FSH/mL after reconstitution with sterile saline. Bravelle contains up to 2% luteinizing hormone (LH) activity based on bioassay. Bravelle is indicated for ovulation induction.

The drug substance, purified urofollitropin (FSH), is a natural glycoprotein hormone isolated from urine obtained from post-menopausal women. FSH contains two different peptide subunits [redacted] (including carbohydrate). The alpha protein subunit contains 92 amino acids and the beta protein subunit contains 111 amino acids. The proposed drug product formulation was used for all clinical studies.

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

The dose used must be individualized for each patient by a physician experienced in providing fertility treatments. The lowest dose consistent with achieving good results based on clinical experience should be used. The recommended initial dose is 150 IU daily for the first five days. Bravelle is supplied in a sterile, lyophilized, single dose vial containing 82.5 IU of FSH, to deliver 75 IU FSH after reconstituting with diluent. Each vial is available with an accompanying vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP. The maximum daily dose is 450 IU FSH. The proposed expiration period is 24 months stored at refrigerated or room temperature.

C. Basis for Approvability or Not-Approval Recommendation

This administrative NDA cross-references all CMC information to the approved NDA 21-289, for Bravelle (urofollitropin for injection, purified). There are no CMC changes, therefore, no chemistry review is required. From a chemistry viewpoint, the NDA is approvable.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

Martin Haber, Ph.D./Date: Same date as draft review
Duu-Gong Wu, Ph.D./Date
Archana Reddy/Date

C. CC Block

See DFS

Chemistry Assessment

Background Information:

This is a consult review for HFD-580. This NDA provides for **Bravelle (urofollitropin for injection, purified)** drug product containing highly purified urofollitropin (urinary FSH).

This administrative NDA cross-references all CMC information to the approved NDA 21-289, for Bravelle (urofollitropin for injection, purified). There are no CMC changes. Therefore, no chemistry review is required.

The User Fee Date for the submission is 12/19/02. Satisfactory EER was received on 10/8 02. For specific chemistry comments, see Review notes and Chemistry Review Summary.

I. DRUG SUBSTANCE **Satisfactory, see NDA 21-289 reviews**

II. DRUG PRODUCT **Satisfactory, see NDA 21-289 reviews**

III. INVESTIGATIONAL FORMULATIONS **Satisfactory**

The approved drug product (NDA 21-289) was used for all studies.

IV. ENVIRONMENTAL ASSESSMENT **Satisfactory, see NDA 21-289 reviews**

V. METHODS VALIDATION NA

This is an administrative NDA, method validation will be done for NDA 21-289.

VI. LABELING NA

Chemistry section of labeling has not changed.

VII. ESTABLISHMENT INSPECTION Satisfactory, see attachments

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

Executive Summary Section

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21484/000 Sponsor: FERRING PHARMS

Org Code : 580 120 WHITE PLAINS RD STE 400

Priority : S TARRYTOWN, NY 10591

Stamp Date : 19-FEB-2002 Brand Name : BRAVELLE (PURIFIED

PDUFA Date : 19-DEC-2002 UROFOLLITROPIN) 75IU

Action Goal : Estab. Name:

District Goal: 20-OCT-2002 Generic Name: PURIFIED UROFOLLITROPIN

Dosage Form: (FOR INJECTION)

Strength : 75 IU

FDA Contacts: A. REDDY Project Manager (HFD-580) 301-827-5424

M. HABER Review Chemist (HFD-510) 301-827-6420

Overall Recommendation: ACCEPTABLE on 08-OCT-2002by J. D AMBROGIO(HFD-324) 301-827-0062

WITHHOLD on 03-SEP-2002by J. D AMBROGIO(HFD-324) 301-827-0062

Establishment : CFN FEI :

DMF No: AADA:

Responsibilities:

Profile : SVT OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-OCT-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

CHEMISTRY REVIEW

Executive Summary Section

DMF No: AADA:

Responsibilities:

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	30-JUL-02		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

Establishment : CFN FEI :

DMF No: AADA:

22-OCT-2002 FDA CDER EES Page 2 of 3

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-MAY-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CEX OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-MAY-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-SEP-02
Decision : ACCEPTABLE

CHEMISTRY REVIEW

Executive Summary Section

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1643045 FEI : 1643045

SP PHARMACEUTICALS LLC

4200 4272 BALLOON PARK ROAD NE

ALBUQUERQUE, NM 87109

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAY-02

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

22-OCT-2002 FDA CDER EES Page 3 of 3

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : SVL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JUN-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : SVL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-MAY-02

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

VIII. DRAFT DEFICIENCY LETTER NA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Martin Haber
10/31/02 04:38:36 PM
CHEMIST

recommends approval

Duu-gong Wu
10/31/02 05:19:56 PM
CHEMIST

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

Environmental Assessment

This new drug application qualifies for an environmental assessment waiver. Refer to chemistry review for NDA 21-289 for Bravelle.

12/08/02

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

Methods Validation

Methods Validation will be requested upon approval of this new drug application.

AR 12/08/02

Bravelle™ (urofollitropin for injection, purified)
Ferring Pharmaceuticals, Inc.
NDA 21-484

DMF Review

This is part of the chemistry review for this new drug application.

ark 12/08/02