CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-663

Chemistry Review(s)

NDA 21-663

Menopur Injection

Ferring Pharmaceuticals Inc.

Martin Haber, Ph.D.
Division of Metabolism and Endocrine Drug Products

Consult Review For:
Division of Reproductive and Urologic Drug Products

Table of Contents

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Chemistry Review Data Sheet

1. NDA 21-663

2. REVIEW #: 2

3. REVIEW DATE: October 22, 2004

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA (10 Volumes)	12/28/03
Initial CMC Filing Memorandum	2/26/04
Amendment (response to Filing comments)	5/10/04
FDA CMC IR Letter	7/30/04
Chemistry Review #1	8/6/04

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (response to teleconference)	8/3/04
Amendment (response to Biopharm request)	8/5/04
Amendment (response to FDA CMC IR letter)	8/10/04

7. NAME & ADDRESS OF APPLICANT:

Name:	Ferring Pharmaceuticals Inc.
Address:	400 Rella Boulevard, Suite 300, Suffern, NY 10901
Representative:	James Conover, Ph.D.
Telephone:	845-770-2600

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Menopur
b) Non-Proprietary Name (USAN): Menotropins for Injection, USP
c) Code Name/# (ONDC only): Purified Repronex
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Fertility: [ ]

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: Single dose vial 75 IU of FSH and LH

13. ROUTE OF ADMINISTRATION: SC or IM Injection

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Human menopausal gonadotropins (HMG) preparation containing approximately equal amounts of follicle stimulating hormone (FSH) and luteinizing hormone (LH) activity extracted from the urine of postmenopausal women. FSH and LH are both acidic glycoproteins, each consisting of two subunits of about 25 kDa molecular weight, including carbohydrates. The common α subunit contains 92 amino acids. The β subunits are unique to each hormone, the β subunits of FSH and LH contain 111 and 121 amino acids, respectively. Another acidic glycoprotein, human Chorionic Gonadotropin (hCG) is also present in the drug substance and it contributes to the LH activity. The β subunit of the hCG glycoprotein contains 145 amino acids. Other urinary proteins are also present as impurities; however, this NDA preparation is about 25-fold more purified than traditional menotropins preparations.

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	REVIEWER/ COMMENTS
—	III	—	—	3	Adequate	10/22/99	Dr. Harapanhalli, NDA 21092
—	III	—	—	3	Adequate	1/4/01	Dr. Powers, ANDA 74802
—	II	—	HMG	3	Adequate	1994	Dr. C-H. Niu, ANDA 73598

[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	53,954	Repronex (Menotropins for injection, USP)
NDA	21-047	Repronex (Menotropins for injection, USP)
NDA	21-289/484	Bravelle (Urofollitropin for injection, purified)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
Methods Validation	Pending		
ODS/DMETS	Tradename Acceptable	2/10/04	L. Wisniewski
EA	Categorical exclusion granted	10/22/04	M. Haber
Microbiology	Approval	10/5/04	J. McVey

The Chemistry Review for NDA 21-663

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval pending an acceptable cGMP inspection status.

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

NA

II. Summary of Chemistry Assessments

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

The Menopur drug product contains 75 IU of FSH activity and 75 IU of LH activity in a sterile, lyophilized preparation in a glass vial with a rubber stopper and metal overseal. The excipients are — mg of lactose, 5 mcg of polysorbate 20 and small traces of sodium phosphate for pH adjustment. The drug product is manufactured by Cardinal Health, Albuquerque, NM. The bulk solution is [ ]

The drug substance is a [ ] purified extract from the urine of postmenopausal and menopausal women that contains the gonadotropin hormones, FSH, LH and hCG. Hormone activity for FSH and LH is measured in International Units using rat bioassays relative to an international reference standard. The drug substance is manufactured by [ ] [ ] from urine collected from about — women donors living around — The drug substance is more purified than the currently marketed menotropins product, therefore the amount of contaminating urinary proteins is much reduced (about 25-fold).

Both FSH and LH are purified through [ ] The FSH and LH activity ratio is adjusted to about 1:1 by [ ]

The drug substance quality is mainly controlled by bioassay testing for FSH and LH activity and measurement of the protein content. The percent aggregation is

limited to NMT — Specifications also include microbial bioburden and viral safety testing. The drug substance has been shown to be stable for 48 months at 2-8°C, the recommended storage temperature.

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

Menopur is indicated fo[redacted] The dose used must be individualized for each patient by a physician experienced in providing fertility treatments. The drug product is a sterile, lyophilized, single-dose preparation in a glass vial containing 75 IU of FSH and 75 IU of LH bioactivity. Only one strength is proposed. The package also contains a 2 mL vial of 0.9% Sodium Chloride Injection, USP, diluent for use in reconstituting the solution for SC or IM injection. The expiration period is 24 months stored at refrigerated or room temperature.

C. Basis for Approvability or Not-Approval Recommendation

The firm has provided adequate chemistry manufacturing and controls information. The manufacturing processes for both drug substance and product are adequately described. The specifications for both drug substance and product are adequate. The drug product stability is adequate to support an expiry date of 24 months at either refrigerated or room temperature. A product quality microbiology review dated 10/5/04 found the application acceptable. The application is acceptable from a chemistry viewpoint, pending an acceptable and the status of cGMP inspections.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

8 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Martin Haber
10/22/04 04:06:33 PM
CHEMIST

approval pending acceptable EER

Moo-Jhong Rhee
10/26/04 02:29:01 PM
CHEMIST
I concur

NDA 21-663

Menopur Injection

Ferring Pharmaceuticals Inc.

Martin Haber, Ph.D.
Division of Metabolism and Endocrine Drug Products

Consult Review For:
Division of Reproductive and Urologic Drug Products

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Chemistry Review Data Sheet

1. NDA 21-663

2. REVIEW #: 1

3. REVIEW DATE: August 5, 2004

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Initial CMC Filing Memorandum	2/26/04

6. SUBMISSION(S) BEING REVIEWED:

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- Submission Priority: S

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NDA	21-289	Bravelle (Urofollitropin for injection, purified)

18. STATUS:

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EES	Pending		
Pharm/Tox	NA		
Biopharm	NA		
Methods Validation	Pending		
ODS/DMETS	Tradename Acceptable	2/10/04	L. Wisniewski
EA	Categorical exclusion granted		
Microbiology	Pending		J. McVey

The Chemistry Review for NDA 21-663

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend Approval pending a satisfactory response to requests for additional chemistry information, and acceptable microbiology review and cGMP inspection status.

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

NA

II. Summary of Chemistry Assessments

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

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C. Basis for Approvability or Not-Approval Recommendation

The firm has provided adequate chemistry manufacturing and controls information. The manufacturing processes for both drug substance and product are adequately described. The specifications for both drug substance and product are adequate. The drug product stability is adequate to support an expiry date of 24 months at either refrigerated or room temperature. The application is acceptable from a chemistry viewpoint, pending an adequate response to the comments delineated in Section VIII of the Chemistry Assessment. In addition, microbiology review and the status of cGMP inspections are pending.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Martin Haber
8/6/04 11:38:53 AM
CHEMIST

Moo-Jhong Rhee
8/6/04 02:50:01 PM
CHEMIST
I concur

NDA 21-663

Menopur® (menotropins for injection USP)

Ferring Pharmaceuticals

Project Manager
Martin Kaufman
HFD-580
301-827-4234

Environmental Assessment

Please refer to page 55 of the August 5, 2004 Chemistry Review

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products

Memorandum

Date: October 27, 2004

From: Martin Haber, Ph.D., Review Chemist, HFD-510

Subject: Establishment Evaluation

To: NDA 21-663 Menopur

Chemistry Review #2, dated 10/22/04, recommended approval for NDA 21-663 from a chemistry viewpoint, pending a recommendation regarding the cGMP inspection status of the manufacturing facilities by the Office of Compliance (OC). An establishment evaluation from the OC for the NDA has now been received, see attachment. The cGMP status of all facilities is acceptable. Therefore, the overall recommendation from chemistry for the NDA is approval.

R/D Init by: Dr. M-J. Rhee, Chemistry Team Leader

Orig. NDA 21-663
cc: HFD-580/Division file/M.Haber/

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21663/000
Org Code : 580
Priority : 3S

Sponsor: FERRING
400 RELLA BLVD STE 300
SUFFERN, NY 10901

Stamp Date : 29-DEC-2003
PDUFA Date : 29-OCT-2004
Action Goal :
District Goal: 30-AUG-2004

Brand Name : MENOPUR (MENOTROPINS)
INJECTION 75IU
Estab. Name:
Generic Name: MENOTROPINS
Dosage Form: (FOR INJECTION)
Strength : 75 IU FSH/ 75 IU LH

FDA Contacts:			
M. KAUFMAN	Project Manager	(HFD-580)	301-827-4260
M. HABER	Review Chemist	(HFD-510)	301-827-6420
M. RHEE	Team Leader	(HFD-580)	301-827-4237

Overall Recommendation: ACCEPTABLE on 27-OCT-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-FEB-04
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI

DMF No: AADA:

Responsibilities:

Profile : OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-FEB-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-FEB-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 1643045 FEI : 1643045

CARDINAL HEALTH MANUFACTURING SERVICES B V

4200 4272 BALLOON PARK ROAD NE

ALBUQUERQUE, NM 87109

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE MANUFACTURER

Profile : SVL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 13-FEB-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-FEB-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-OCT-04

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-FEB-04

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

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/s/

Martin Haber
10/27/04 03:01:59 PM
CHEMIST

Moo-Jhong Rhee
10/27/04 04:24:39 PM
CHEMIST
I concur

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

Methods Validation

10/29/04

Not yet requested.