? 1047/5001

27

NDA 21-047/S-001

JUL 21 2000

Ferring Pharmaceuticals, Inc.
Attention: Ronald V. Nardi, Ph.D.
Vice President, Regulatory & Scientific Affairs
120 White Plains Road, Suite 409
Tarrytown, NY 10591

Dear Dr. Nardi:

Please refer to your supplemental new drug application dated January 14, 2000, received January 18, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Repronex® (menotropins for injection, USP) 75 or 150 IU.

We acknowledge receipt of your submissions dated May 11 and June 5, 2000.

This supplemental new drug application provides for changes to the **DESCRIPTION** section, the **CLINICAL PHARMACOLOGY** section, **Clinical Studies** subsection, and the **CONTRAINDICATIONS, WARNINGS** and **ADVERSE REACTIONS** sections of the package insert to clarify the number of patients receiving Repronex in the clinical trials reported in the package insert and to correct some minor typographical errors.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 5, 2000, and immediate container and carton labels submitted January 14, 2000).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-047/S-001." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Diane Moore, BS, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA/21-047/S-001
HFD-580/Div. Files
HFD-580/D.Moore/TRumble
HFD-580/SAllen/MMann/SSlaughter/RBennett/MRhee
HFD-580/AJordan/AParekh/LKammerman
HFD-510/MHaber
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-42/DDMAC (with labeling)

HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director/JGibbs
DISTRICT OFFICE
Drafted by: dm/June 28, 2000
Initialed by: TRumble 7.3.00/RBennett, SSlaughter, MRhee 7.6.00/MMann 7.10.00/SAllen 7.18.00
final: July 19, 2000

APPROVAL (AP)

APPEARS THIS WAY
ON ORIGINAL

JUL 12 2000

DA 21-047

Labeling review
Repronex® (menotropins for injection)
Material Reviewed: Package Insert and Container and Carton label for 75 IU strength
Submission Date: January 14, 2000
Amendment Date: May 11, 2000
Amendment Date: June 5, 2000
Date approved:
Deletions denoted by ~~strikeouts~~
Additions denoted by highlighting

Currently Approved Labeling	Proposed Revisions	Medical Officer Comments
DESCRIPTION Repronex® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each vial of Repronex® contains 75 International Units (IU) or 150 IU of follicle-stimulating hormone (FSH) activity and 75 IU or 150 IU of luteinizing hormone (LH) activity, respectively, plus 20 mg lactose monohydrate in a sterile, lyophilized form. The final product may contain sodium phosphate buffer (sodium phosphate tribase ı phosphoric acid). Repronex® is ıinistered by subcutaneous or ıntramuscular injection. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in post-menopausal urine, is detected in Repronex®.	**DESCRIPTION** Repronex® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each vial of Repronex® contains 75 International Units (IU) or 150 IU of follicle-stimulating hormone (FSH) activity and 75 IU or 150 IU of luteinizing hormone (LH) activity, respectively, plus 20 mg lactose monohydrate in a sterile, lyophilized form. The final product may contain sodium phosphate buffer (sodium phosphate tribasic and phosphoric acid). Repronex® is administered by subcutaneous or intramuscular injection. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in post-menopausal urine, is detected in Repronex®.	The word revision is acceptable.
CLINICAL PHARMACOLOGY	**CLINICAL PHARMACOLOGY** NC	
CLINICAL STUDIES Efficacy results for two randomized, active controlled, multi-center studies in *in vitro* fertilization (IVF) and ovulation induction (OI) are summarized in tables 2 and 3. The patients underwent pituitary suppression with a GnRH agonist before starting Repronex® administration. The first study evaluated 186 patients undergoing IVF who received 225 IU Repronex® daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed 12 days. The second study evaluated 108 patients who received 150 IU Repronex® daily for 5 days. This was followed by individual titration of the dose ɔm 75 to 450 IU daily based on ɹasound and estradiol (E_2) levels. The	**CLINICAL STUDIES** Efficacy results ~~for two randomized, active controlled, multi-center studies~~ results from a clinical trial in *in vitro* fertilization (IVF) patients and a clinical trial in ovulation induction (OI) in anovulatory and oligovulatory patients are summarized in tables 2 and 3. ~~Both studies were multicenter, active control, randomized, parallel group designs.~~ In addition, all ~~The~~ patients in both studies underwent pituitary suppression with a GnRH agonist before starting treatment with Repronex® or the control therapy administration. The ~~first~~ IVF study evaluated 186 patients (~~125 patients received Repronex®). undergoing IVF who~~ The patients treated with Repronex® received 225 IU Repronex® daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound	The proposed revisions are acceptable. Note: multicenter should be hyphenated as follows: multi-center.

days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration (see PRECAUTIONS – Laboratory Tests), the hCG should be withheld.	common, more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore, patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration (see **PRECAUTIONS – Laboratory Tests**), the hCG should be withheld.	In the phrases, "(see PRECAUTIONS – Laboratory Tests)," the words, "**Laboratory Tests**" should be bolded.
PRECAUTIONS **Laboratory Tests** The clinical confirmation of ovulation, is determined by:	**PRECAUTIONS** NC	The comma after the word ovulation is not needed and should be deleted.
ADVERSE REACTIONS **Table 4: Patients with Adverse Events ≥1%** GENITOURINARY?REPRODUCTIVE AEs OHSS ~~1(1.0)~~ 3(3.0) Breast Tenderness ~~1(2.0)~~ 2(2.1) GASTROINTESTINAL AEs Diarrhea 0 2(2.21) "HER BODY SYSTEM AEs :tion 1(1.0) 0 Fisher's Exact/Chi-Squared Tests-significant for Repronex™ v. Repronex™ IM.	**ADVERSE REACTIONS** **Table 4: Patients with Adverse Events ≥1%** GENITOURINARY?REPRODUCTIVE AEs OHSS ~~2(2.0)~~ ~~5(5.2)~~ Breast Tenderness ~~2(2.0)~~ 2(2.1) GASTROINTESTINAL AEs Diarrhea 0 ~~(0)~~ 2(2.21) OTHER BODY SYSTEM AEs Infection 1(1.0) 0 ~~(0)~~ Fisher's Exact/Chi-Squared Tests-significant for Repronex™ ~~(0)~~ v. Repronex™ ~~(0)~~ IM.	The revised numbers are more accurate than the previous numbers in the table. The trademark symbol ™ was replaced by the registered trademark symbol ®. The revisions are acceptable.
OVERDOSAGE	**OVERDOSAGE** NC	
DOSAGE AND ADMINISTRATION If patient response to Repronex® is appropriate, hCG (5000 to 10,000 USP units) . . . If there is inadequate follicle development or ovulation without subsequent pregnancy, the course of treatment with Repronex may be repeated.	**DOSAGE AND ADMINISTRATION** If patient response to Repronex® is appropriate, hCG (5000 to 10,000 USP units) . . . If there is inadequate follicle development or ovulation without subsequent pregnancy, the course of treatment with Repronex® may be repeated	The trademark symbol ® has been inserted. This is acceptable.
HOW SUPPLIED	**HOW SUPPLIED** NC	

There were no changes to the 75 IU carton or container. No mock-ups of the 150 IU label were provided. Draft or mock-ups of the 150 IU carton and container should be submitted.

See next page.

Repronex® Package Insert and Container and Carton Review
Date received: January 14, 2000
Revisions: May 11 and June 5, 2000

Proposed Regulatory Action (MO to complete):

X Approval
Approvable with the following modifications:

Not Approvable (provide rationale)

7/6/00
CSO/PM signature Date

7/11/00
Chief, Project Management Staff Date

7/6/00
Medical Officer Signature Date

7/10/00
Medical Team Leader Date

7/12/00
Deputy Director Concurrence Date

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-047/SLR-001

Ferring Pharmaceuticals Inc.
120 White Plains Road, Suite 400
Tarrytown, NY 10591

MAY 19 2000

Attention: Ronald V. Nardi, Ph.D.
Vice President, Sciencetific & Regulatory Affairs

Dear Dr. Nardi:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Repronex®
NDA Number:	21-047
Supplement Number:	SLR-001
Date of Supplement:	January 14, 2000
Date of Receipt:	January 18, 2000

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on March 18, 2000 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 21-047/SLR-001
HFD-580/Div. Files
HFD-580/CSO/D. Moore

SUPPLEMENT ACKNOWLEDGEMENT

CSO USER FEE VALIDATION SHEET

NDA # 21-047 Document ID # SLR-001 UFID # _____

Letter Date January 14, 2000 Division HFD-580 (DRUDP)

CSO Diane Moore

Drug Name Repronex

Sponsor Ferring Pharmaceuticals

1. (YES) NO **User Fee Cover Sheet Validated?** **MIS_Elements Screen Change(s):**

2. YES (NO) **APPLICATION CONTAINS CLINICAL DATA?**
(Circle YES if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., to add an adverse reaction, contraindication or warning to the labeling)

REF **IF NO CLINICAL DATA IN SUBMISSION, INDICATE IF CLINICAL DATA ARE CROSS REFERENCED IN ANOTHER SUBMISSION.**

3. YES (NO) **SMALL BUSINESS EXEMPTION**

4. YES (NO) **WAIVER GRANTED**

5. YES (NO) **NDA BEING SPLIT FOR ADMINISTRATIVE CONVENIENCE (other then bundling).**
If **YES**, list all NDA #s, review division(s) and those for which an application fee applies.

NDA #	Division		
N_____	HFD-_____	Fee	No Fee
N_____	HFD-_____	Fee	No Fee

6. (YES) NO **BUNDLING POLICY APPLIED CORRECTLY? No Data Entry Required**
(Circle YES if application is properly designated as one application or is properly submitted as a supplement instead of an original application. Circle NO if application should be split into more than one application or be submitted as an original instead of a supplement. If NO, list resulting NDA #s and review division(s)

NDA #	Division	NDA #	Division
N_____	HFD-_____	N_____	HFD-_____

7. P (S) **PRIORITY or STANDARD APPLICATION?**

/S/ 1/14/00 /S/ 5/19/00

CSO Signature / Date SPM Concurrence Signature / Date

FERRING
PHARMACEUTICALS

January 14, 2000

Susan Allen, MD
Acting Director, Division of Reproductive
and Urologic Drugs
US Food and Drug Administration
Parklawn Building, HFD-580
5600 Fishers Lane
Rockville, MD 20857

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JAN 18 2000
HFD-580

NDA NO. 21047 REF. NO. S-001
NDA SUPPL FOR labelling

OHC Amendment

RE: Repronex® NDA #21,047
Final Printed Labeling

Dear Ms. Moore:

Enclosed please find the Final Printed Labeling and Final Packaging for Repronex® approved under the above referenced NDA. Please note that the final printed labeling contains corrections of minor errors discovered after the package insert was approved. They are:

- Minor typographical changes.
- Per discussion with FDA, the OHSS section was modified to include the explicit data from the clinical trials.
- Per discussion with FDA, the Adverse Event Table numbers were corrected to reflect the data from both clinical trials.

A color revised-text version is included in this submission to clarify where the changes have been made.

If you require any additional information, please contact me at 914-333-8932.

Sincerely,

Ronald V. Nardi

Ronald V. Nardi, Ph.D.
Vice President, Scientific & Regulatory Affairs

REVIEWS COMPLETED
CSO INITIALS
LETTER
CSO INITIALS
DATE

RVN:mgc

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U S A
Telephone· (914) 333-8900, Telefax: (914) 631-1992

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED | DATE FILED

DIVISION ASSIGNED | NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314)

NAME OF APPLICANT

FERRING PHARMACEUTICALS INC.

DATE OF SUBMISSION:

January 13, 2000

ADDRESS (Number, Street, City, State, and Zip Code)

120 White Plains Road, Suite 400
Tarrytown, NY 10591

TELEPHONE NO. (Include Area Code)

(914)333-8900

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

21047

DRUG PRODUCT

ESTABLISHED NAME (e.g. USP/USAN)	PROPRIETARY NAME (If any)
Menotropins for Injection	Repronex™

CODE NAME (If any)	CHEMICAL NAME
None	Extract of Human Postmenopausal Urine Containing Both Follicle Stimulating Hormone and Lutenizing Hormone (ISAN)

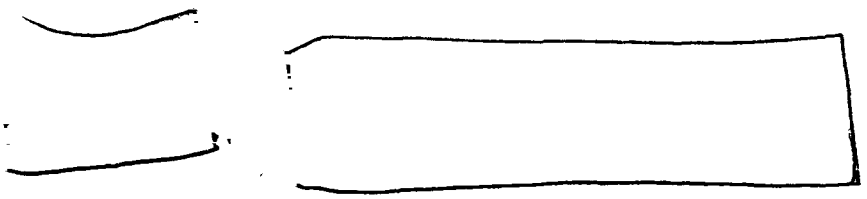
DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Injection	Intramuscular/Subcutaneous	75 IU/vial 150 IU/Vial

PROPOSED INDICATIONS FOR USE

WOMEN: For the induction of ovulation and pregnancy in the anovulatory infertile patient, and stimulate the development of multiple follicles in ovulatory patients participating in an invitro fertilization program.

MEN: For the stimulation of spermatogenesis in men who have primary or secondard hypogonadotropic hypogonadism.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR PART 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR PART 314), AND DRUG MASTER FILES (21 CFR 314.20) REFERRED TO IN THIS APPLICATION:



INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION (21CFR 314.50

☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21CFR 314.55

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ORIGINAL APPLICATION

☐ ☒ AN AMENDMENT TO A PENDING APPLICATION

☐ RESUBMISSION

☐ SUPPLEMENTAL APPLICATION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)

☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION	
This application contains the following items: (Check all that apply)	
	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d)(1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
	i. draft labeling (4 copies)
X	ii. Final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER (Specify)

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulation that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Ronald V. Nardi, Ph.D Vice President, Regulatory & Scientific Affairs	Ronald V. Nardi	1/13/2000

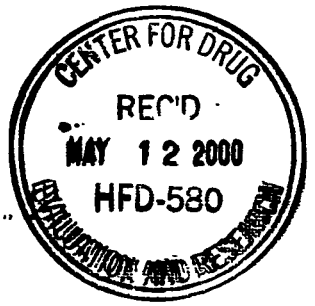
ADDRESS (Street, City, State, Zip Code)	TELEPHONE NO. (Include Area Code)
120 White Plains Road, Suite 400 Tarrytown, NY 10591	(914) 333-8900

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FERRING
PHARMACEUTICALS

May 11, 2000

ORIGINAL



BL

NDA SUPP AMEND
S-001

Susan Allen, MD
Acting Director, Division of Reproductive
and Urologic Drugs
US Food and Drug Administration
Parklawn Building, HFD-580
5600 Fishers Lane
Rockville, MD 20857

RE: Repronex® NDA #21,047/S001

NDA 21-047 SUP-001
NDA Labeling.

Dear Dr. Allen:

Enclosed please find the above referenced supplemental NDA which contains changes to the package insert requested by your division. The changes clarify the number of patients receiving Repronex® in the clinicals reported in the package insert (see page 4). A color revised-text version is included in this submission to clarify where the changes have been made.

Upon approval of this supplement, these changes will be incorporated into our Final Printed Labeling.

If you require any additional information, please contact me at 914-333-8932.

Sincerely,

Ronald V. Nardi, Ph.D.
Vice President, Scientific & Regulatory Affairs

RVN:mgc

Enclosure: S001

REVIEWS COMPLETED
CSO ACTION
☑ LETTER ☐ FINAL LABELING
INITIALS DATE

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED | DATE FILED

DIVISION ASSIGNED | NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314)

NAME OF APPLICANT
FERRING PHARMACEUTICALS INC.

DATE OF SUBMISSION:
May 11, 2000

ADDRESS (Number, Street, City, State, and Zip Code)
120 White Plains Road, Suite 400
Tarrytown, NY 10591

TELEPHONE NO. (Include Area Code)
(914)333-8900

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)
21047

DRUG PRODUCT

ESTABLISHED NAME (e.g. USP/USAN)	PROPRIETARY NAME (If any)
Menotropins for Injection	Repronex™

CODE NAME (If any)	CHEMICAL NAME
None	Extract of Human Postmenopausal Urine Containing Both Follicle Stimulating Hormone and Lutenizing Hormone (ISAN)

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Injection	Intramuscular/Subcutaneous	75 IU/vial 150 IU/Vial

PROPOSED INDICATIONS FOR USE

WOMEN: For the induction of ovulation and pregnancy in the anovulatory infertile patient, and stimulate the development of multiple follicles in ovulatory patients participating in an invitro fertilization program.

MEN: For the stimulation of spermatogenesis in men who have primary or secondard hypogonadotropic hypogonadism.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 *CFR* PART 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 *CFR* PART 314), AND DRUG MASTER FILES (21 *CFR* 314.20) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

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☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☒ SUPPLEMENTAL APPLICATION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)
☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION	
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[redacted]	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling (4 copies)
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	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
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3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	DATE
Ronald V. Nardi, Ph.D Vice President, Regulatory & Scientific Affairs	Ronald V. Nardi	5/10/00

ADDRESS (Street, City, State, Zip Code)

120 White Plains Road, Suite 400
Tarrytown, NY 10591

TELEPHONE NO. (Include Area Code)

(914) 333-8900

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

FERRING

PHARMACEUTICALS

June 5, 2000

Susan Allen, MD
Acting Director, Division of Reproductive
and Urologic Drugs
US Food and Drug Administration
Parklawn Building, HFD-580
5600 Fishers Lane
Rockville, MD 20857

NDA SUPP AMEND
SLR-001-BL

RE: Repronex® NDA #21,047/ Amendment to S001 (dated 5/11/00)

Dear Dr. Allen:

Enclosed please find the above referenced supplemental NDA which contains changes to the package insert requested by your division. The changes clarify the number of patients receiving Repronex® in the clinicals reported in the package insert (see page 4). A color revised-text version is included in this submission to clarify where the changes have been made.

Upon approval of this supplement, these changes will be incorporated into our Final Printed Labeling.

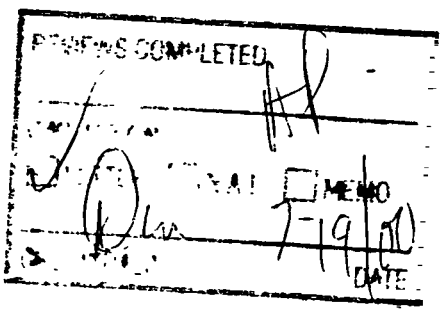
If you require any additional information, please contact me at 914-333-8932.

Sincerely,

Ronald V. Nardi, Ph.D.
Vice President, Scientific & Regulatory Affairs

RVN:mgc

Enclosure: S001



Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
Telephone: (914) 333-8900, Telefax: (914) 631-1992

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: December 31, 1992
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED | DATE FILED

DIVISION ASSIGNED | NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314)

NAME OF APPLICANT

FERRING PHARMACEUTICALS INC.

DATE OF SUBMISSION:

June 5, 2000

ADDRESS (Number, Street, City, State, and Zip Code)

120 White Plains Road, Suite 400
Tarrytown, NY 10591

TELEPHONE NO. (Include Area Code)

(914)333-8900

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)

21047

DRUG PRODUCT

ESTABLISHED NAME (e.g. USP/USAN)	PROPRIETARY NAME (if any)
Menotropins for Injection	Repronex™

CODE NAME (if any)	CHEMICAL NAME
None	Extract of Human Postmenopausal Urine Containing Both Follicle Stimulating Hormone and Lutenizing Hormone (ISAN)

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Injection	Intramuscular/Subcutaneous	75 IU/vial 150 IU/Vial

PROPOSED INDICATIONS FOR USE

WOMEN: For the induction of ovulation and pregnancy in the anovulatory infertile patient, and stimulate the development of multiple follicles in ovulatory patients participating in an invitro fertilization program.

MEN: For the stimulation of spermatogenesis in men who have primary or secondard hypogonadotropic hypogonadism.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 *CFR* PART 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 *CFR* PART 314), AND DRUG MASTER FILES (21 *CFR* 314.20) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION (21CFR 314.50

☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21CFR 314.55

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION
☐ ORIGINAL APPLICATION
☐ AN AMENDMENT TO A PENDING APPLICATION
☐ RESUBMISSION
☒ SUPPLEMENTAL APPLICATION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx)

☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION	
This application contains the following items: (Check all that apply)	
	1. Index
	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d)(1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
[redacted]	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling (4 copies)
	ii. Final printed labeling (12 copies)
	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
	7. Microbiology section (21 CFR 314.50 (d) (4))
	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER (Specify)

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulation that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

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Ronald V. Nardi, Ph.D Vice President, Regulatory & Scientific Affairs	Ronald V. Nardi	6/5/00

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Original

Label
NDA No. 21-047 1-14-00
Reviewed by: Qua 4/13/00

REXAM
1

6040-01
UK 22709-1

N 3 55566-7185-2 5

Manufactured For:
Ferring Pharmaceuticals Inc., Tarrytown, NY 10591
By: Lederle Parenterals, Inc., Carolina, Puerto Rico 00987
Diluent manufactured for Ferring Pharmaceuticals Inc.

FOR SUBCUTANEOUS AND INTRAMUSCULAR INJECTION ONLY

FERRING
PHARMACEUTICALS

APPROVED
JUL 21 2000

Repronex® 75
(menotropins for injection, USP)
75 IU FSH, 75 IU LH

FOR SUBCUTANEOUS AND INTRAMUSCULAR INJECTION ONLY

5 single dose vials of Menotropins for injection, USP, and
5 single dose vials of 0.9% Sodium Chloride Injection, USP, 2 mL.

NDC 55566-7185-2

5 single dose vials of Menotropins for injection, USP, and
5 single dose vials of 0.9% Sodium Chloride Injection, USP, 2 mL.

FOR SUBCUTANEOUS AND INTRAMUSCULAR INJECTION ONLY
Reconstitute with 1 to 2 mL 0.9% Sodium Chloride Injection, USP.

Administer SC or IM immediately after reconstitution.
Discard unused portion.

Usual Dosage. See package circular for dosage and complete prescribing information

Lyophilized powder may be stored refrigerated or at room temperature (3° to 25° C/37° to 77° F)
Protect from light

NDC 55566-7185-2

Repronex® 75

(menotropins for injection, USP)

75 IU FSH, 75 IU LH

FOR SUBCUTANEOUS AND INTRAMUSCULAR INJECTION ONLY

CONTENTS Each single dose vial of sterile, lyophilized menotropins contains:
75 IU of FSH
75 IU of LH
lactose monohydrate 20 mg.
May contain sodium phosphate buffer (sodium phosphate tribasic and phosphoric acid).
Each single dose vial of diluent contains 2 mL 0.9% Sodium Chloride Injection, USP.

Rx only

FERRING PHARMACEUTICALS

Control No.

Exp. Date

Labeling: Original

NDA No. 21-047 1-14-00

Reviewed: DM 4/13/00

Repronex

(menotropins for i

75 IU FSH 75 IU LH

FOR SUBCUTANEOUS

INJECTION ONLY

SINGLE DOSE VIAL

Discard unused por

NDC 55566-7185-0

JUL 21 2000

Repronex® 75

(menotropins for injection, USP)

75 IU FSH, 75 IU LH

FOR SUBCUTANEOUS AND INTRAMUSCULAR

INJECTION ONLY

SINGLE DOSE VIAL

Discard unused portion.

Rx only

NDC 55566-7185-0

Control No.

Exp. Date

U7185-00-1

APPROVED

JUL 21 2000

Repronex® 75
(menotropins for injection, USP)
75 IU FSH, 75 IU LH
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INJECTION ONLY
SINGLE DOSE VIAL
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Rx only
NDC 55566-7185-0
APPROVED
JUL 21 2000

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JUL 21 2000

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APPROVED

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(menotropins for injection, USP)
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FOR SUBCUTANEOUS AND INTRAMUSCULAR
INJECTION ONLY
SINGLE DOSE VIAL
Discard unused portion.
Rx only
NDC 55566-7185-0
APPROVED
JUL 2 2000

Labeling: Original
NDA No. 21-047 Rec'd 1-14-00
Reviewed by: DM 4/13/00

CI 6098-1

APPROVED

JUL 2 1 2000

CI 6098-1

CI 6098-1

REPRONEX®
(MENOTROPINS FOR INJECTION, USP)
FOR SUBCUTANEOUS INJECTION AND INTRAMUSCULAR INJECTION

DESCRIPTION

Repronex® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each vial of Repronex® contains 75 International Units (IU) or 150 IU of follicle-stimulating hormone (FSH) activity and 75 IU or 150 IU of luteinizing hormone (LH) activity, respectively, plus 20 mg lactose monohydrate in a sterile, lyophilized form. The final product may contain sodium phosphate buffer (sodium phosphate tribasic and phosphoric acid). Repronex® is administered by subcutaneous or intramuscular injection. Human Chorionic Gonadotropin (hCG), a naturally occurring hormone in post-menopausal urine, is detected in Repronex®.

Repronex® is biologically standardized for FSH and LH (ICSH) gonadotropin activities in terms of the Second International Reference Preparation for Human Menopausal Gonadotropins established in September, 1964 by the Expert Committee on Biological Standards of the World Health Organization.

Both FSH and LH are glycoproteins that are acidic and water soluble. Therapeutic class: Infertility

CLINICAL PHARMACOLOGY

Menotropins administered for 7 to 12 days produces ovarian follicular growth in women who do not have primary ovarian failure. Treatment with menotropins in most instances results only in follicular growth and maturation. When sufficient follicular maturation has occurred, hCG must be given to induce ovulation.

PHARMACOKINETICS

Single doses of 300 IU menotropins (Menogon®, Ferring's European formulation) were administered subcutaneously (SC) and intramuscularly (IM) in a 2-period crossover study to 16 healthy female subjects while their endogenous FSH and LH were being suppressed. Serum FSH concentrations were determined. Based on the ratio of FSH C_{max} and $AUC_{0-\infty}$, SC and IM administration of menotropins are not bioequivalent. Compared to IM administration, the SC administration of menotropins results in an increase of FSH C_{max} and $AUC_{0-\infty}$ by 35 and 20%, respectively.

Based on two subjects who received either the highest SC or IM Repronex® dose, FSH pharmacokinetics (PK) appears to be linear up to 450 IU menotropins. The mean accumulation factors for FSH upon six doses of SC or IM 150 to 450 IU/day Repronex® are 1.6 and 1.4, respectively. Upon six doses of SC or IM 150 IU/day Repronex®, the observed serum FSH concentrations range from 1.7 to 15.9 mIU/mL and 0.5 to 10.1 mIU/mL, respectively. The FSH pharmacokinetic parameters from population modeling for these two studies are in Table 1.

Table 1. FSH Pharmacokinetic Parameters† Upon Menotropins Administration

	Single Dose‡		Multiple Dose¶	
FSH Parameter	SC	IM	SC	IM
K_a (h^{-1})	0.128 (42.1)	0.117 (21.3)	0.076 (46.3)	0.064 (63.2)
Cl/F (L/h)	0.770 (17.1)	0.94 (6.9)	1.11 (39.5)	1.44 (43.5)
V/F (L)	39.37 (14.1)	57.68 (11.4)	23.09 (8.3)	23.5 (2.5)

† mean (CV%)
‡ Menogon® (Ferring's European formulation of menotropins)
¶ Repronex®

Serum LH concentrations upon multiple dose SC or IM Repronex® are low and variable. No recognizable trend in the increase in serum LH concentrations from SC or IM 150 to 450 IU/day Repronex® doses was observed. After the 6th dose of SC or IM 150 IU/day Repronex®, the range of baseline-corrected serum LH concentrations is 0 to 3.2 mIU/mL for both routes of administration.

Absorption

The geometric mean of FSH C_{max} and $AUC_{0-\infty}$ upon single dose SC administration of menotropins is 5.62 mIU/mL and 385.2 mIU·h/mL,

respectively, the corresponding geometric median of FSH t_{max} is 12 hours. The geometric mean of FSH C_{max} and $AUC_{0-\infty}$ upon single dose IM administration of menotropins is 4 15 mIU/mL and 320.1 mIU h/mL, respectively, the corresponding geometric median of FSH t_{max} is 18 hours

Distribution
Human tissue or organ distribution of FSH and LH have not been studied for Repronex®

Metabolism
Metabolism of FSH and LH have not been studied for Repronex® in humans.

Excretion
The mean elimination half-lives of FSH upon single dose SC and IM administration of menotropins are 53 7 and 59 2 hours, respectively

Pediatric Populations
Repronex® is not used in pediatric populations

Geriatric Populations
Repronex® is not used in geriatric populations.

Special Populations
The safety and efficacy of Repronex® in renal and hepatic insufficiency have not been studied

Drug Interactions
No drug/drug interaction studies have been conducted for Repronex® in humans

CLINICAL STUDIES
Efficacy results for two randomized, active controlled, multi-center studies in *in vitro* fertilization (IVF) and ovulation induction (OI) are summarized in tables 2 and 3 The patients underwent pituitary suppression with a GnRH agonist before starting Repronex® administration. The first study evaluated 186 patients undergoing IVF who received 225 IU Repronex® daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol (E_2) levels The total duration of dosing did not exceed 12 days. The second study evaluated 208 patients who received 150 IU Repronex® daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed 12 days.

Table 2. Efficacy Outcomes by Treatment Group for IVF (one cycle of treatment)

Parameter	Repronex® IM N=65	Repronex® SC N=60
Total oocytes Retrieved	13 6	12.7
Mature oocytes Retrieved	9 4	8.6
Pts w/oocyte Retrieval (%)	61(93.8)	55 (91.7)
Pts w/Embryo Transfer (%)	58(89 2)	51(85 0)
Pts w/Chemical Pregnancy (%)	31(47.7)	35(58.3)
Pts w/Clinical Pregnancy (%)	25(38 5)	30(50.0)
Pts w/Continuing Pregnancy (%)	24(36.9) [1]	29(48 3) [2]
Pts w/Live Births (%)	22(33.8) [3]	25(41.7) [4]

Continuing pregnancies included14 single, 7 twins, and 3 triplet pregnancies
Continuing pregnancies included 14 single, 9 twins, 3 triplets, and 3 quadruplet pregnancies
Total of 34 live births One spontaneous abortion The follow-up data is not available for one patient
Total of 39 live births Two spontaneous abortions The follow-up data is not available for two patients

Table 3. Efficacy Outcomes by Treatment Groups in Ovulation Induction (one cycle of treatment)

Parameter	Repronex® IM N=36	Repronex® SC N=36
Ovulation (%)	23 (63 9)	25 (69.4)
Received hCG (%)	25 (69 4)	27 (75.0)
Mean Peak Serum E2 (SD)	1158 5 (742.3)	1452.6* (1270.6)
Chemical Pregnancy (%)	4 (11.1)	11 (30.6)
Clinical Pregnancy (%)	4 (11 1)	6 (16.7)
Continuing Pregnancy (%)	4 (11 1) [1]	6 (16.7) [2]
Pts w/Live Births (%)	4(11.1) [3]	4(11 1) [4]

Fisher's Exact/Chi Squared Tests – significant for Repronex® SC vs Repronex® IM

1 Continuing pregnancies included 2 single and 2 triplet pregnancies
2 Continuing pregnancies included 3 single, 1 twin and 2 quadruplet pregnancies
3 Total 6 live births.
4 Total of 6 live births. One spontaneous abortion The follow-up data is not available for one patient

INDICATIONS AND USAGE
Repronex®, in conjunction with hCG, is indicated for multiple follicular development (controlled ovarian stimulation) and ovulation induction in patients who have previously received pituitary suppression.

Selection of Patients
1. Before treatment with Repronex® is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. Except for those patients enrolled in an *in vitro* fertilization program, this should include a hysterosalpingogram (to rule out uterine and tubal pathology) and documentation of anovulation by means of basal body temperature, serial vaginal smears, examination of cervical mucus, determination of serum (or urine) progesterone, urinary pregnanediol and endometrial biopsy. Patients with tubal pathology should receive menotropins only if enrolled in an *in vitro* fertilization program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3 Careful examination should be made to rule out the presence of an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders Cervical dilation and curettage should always be done for diagnosis before starting Repronex® therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.
5 Evaluation of the husband's fertility potential should be included in the workup

CONTRAINDICATIONS
Repronex® is contraindicated in women who have.
1. A high FSH level indicating primary ovarian failure
2. Uncontrolled thyroid and adrenal dysfunction.
3. An organic intracranial lesion such as a pituitary tumor
4. The presence of any cause of infertility other than anovulation unless they are candidates for *in vitro*-fertilization.
5. Abnormal bleeding of undetermined origin.
6. Ovarian cysts or enlargement not due to polycystic ovary syndrome
7. Prior hypersensitivity to menotropins.
8 Repronex® is not indicated in women who are pregnant. There are limited human data on the effects of menotropins when administered during pregnancy

WARNINGS
Repronex® is a drug that should only be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropic substance capable of causing mild to severe adverse reactions in women. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and its use requires the availability of appropriate monitoring facilities (see **PRECAUTIONS - Laboratory Tests**). In female patients it must be used with a great deal of care.

Overstimulation of the Ovary During Repronex® Therapy
Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 5 to 10% of those treated with Repronex® menotropins and hCG, and generally regresses without treatment within two or three weeks.

In order to minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with Repronex® hCG therapy, the lowest dose consistent with expectation of good results, should be used. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Repronex® therapy, hCG should not be administered in this course of therapy, this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome.

The Ovarian Hyperstimulation Syndrome (OHSS) OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions,

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es by Treatment Group for IVF (one cycle of treatment)

	Repronex® IM	Repronex® SC
	N=65	N=60
	13.6	12 7
	9.4	8 6
	61(93.8)	55 (91.7)
	58(89.2)	51(85.0)
%)	31(47.7)	35(58.3)
	25(38.5)	30(50.0)
(%)	24(36.9) [1]	29(48.3) [2]
	22(33.8) [3]	25(41.7) [4]

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us abortion The follow-up data is not available for one patient
is abortions The follow-up data is not available for two patients

comes by Treatment Groups in Ovulation Induction (one cycle of treatment)

	Repronex® IM	Repronex® SC
	N=36	N=36
	23 (63.9)	25 (69.4)
	25 (69.4)	27 (75.0)
	1158.5 (742.3)	1452.6* (1270 6)
	4 (11 1)	11 (30 6)
	4 (11.1)	6 (16.7)
	4 (11.1) [1]	6 (16.7) [2]
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Repronex® is a drug that should only be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropic substance capable of causing mild to severe adverse reactions in women Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and its use requires the availability of appropriate monitoring facilities (see **PRECAUTIONS - Laboratory Tests**). In female patients it must be used with a great deal of care.

Overstimulation of the Ovary During Repronex® Therapy

Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 5 to 10% of those treated with Repronex® menotropins and hCG, and generally regresses without treatment within two or three weeks.

In order to minimize the hazard associated with the occasional abnormal ovarian enlargement which may occur with Repronex® hCG therapy, the lowest dose consistent with expectation of good results, should be used Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Repronex® therapy, hCG should not be administered in this course of therapy; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome.

The Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event It is characterized by an apparent dramatic increase in vascular permeability which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS· abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see "Pulmonary and Vascular Complications" below) Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with the Ovarian Hyperstimulation Syndrome (OHSS).

OHSS occured in 3 of 125 (2 4%) Repronex® treated women during ART clinical studies None of these cases was classified as severe. In Ovulation Induction clinical studies, 4 of 72 (5 5%) Repronex® treated women developed OHSS and of this number one case was classified as severe (1 4%) Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. OHSS develops rapidly, therefore patients should be followed for at least two weeks after hCG administration Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days following treatment Usually, OHSS resolves spontaneously with the onset of menses If there is evidence that OHSS may be developing prior to hCG administration (see **PRECAUTIONS - Laboratory Tests**), the hCG should be withheld

If OHSS occurs, treatment should be stopped and the patient hospitalized Treatment is primarily symptomatic, consisting of bed rest, fluid and electrolyte management, and analgesics if needed The phenomenon of hemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity, and the pericardial cavity has been seen to occur and should be thoroughly assessed in the following manner 1) fluid intake and output, 2) weight, 3) hematocrit, 4) serum and urinary electrolytes, 5) urine specific gravity, 6) BUN and creatinine, and 7) abdominal girth These determinations are to be performed daily or more often if the need arises

With OHSS there is an increased risk of injury to the ovary. The ascitic, pleural, and pericardial fluid should not be removed unless absolutely necessary to relieve symptoms such as pulmonary distress or cardiac tamponade Pelvic examination may cause rupture of an ovarian cyst, which may result in hemoperitoneum, and should therefore be avoided If this does occur, and if bleeding becomes such that surgery is required, the surgical treatment should be designed to control bleeding and to retain as much ovarian tissue as possible Intercourse should be prohibited in those patients in whom significant ovarian enlargement occurs after ovulation because of the danger of hemoperitoneum resulting from ruptured ovarian cysts

The management of OHSS may be divided into three phases: the acute, the chronic, and the resolution phases Because the use of diuretics can accentuate the diminished intravascular volume, diuretics should be avoided except in the late phase of resolution as described below

Acute Phase Management during the acute phase should be designed to prevent hemoconcentration due to loss of intravascular volume to the third space and to minimize the risk of thromboembolic phenomena and kidney damage Treatment is designed to normalize electrolytes while maintaining an acceptable but somewhat reduced intravascular volume Full correction of the intravascular volume deficit may lead to an unacceptable increase in the amount of third space fluid accumulation Management includes administration of limited intravenous fluids, electrolytes, and human serum albumin. Monitoring for the development of hyperkalemia is recommended.

Chronic Phase After stabilizing the patient during the acute phase, excessive fluid accumulation in the third space should be limited by instituting severe potassium, sodium, and fluid restriction

Resolution Phase A fall in hematocrit and an increasing urinary output without an increased intake are observed due to the return of third space fluid to the intravascular compartment Peripheral and/or pulmonary edema may result if the kidneys are unable to excrete third space fluid as rapidly as it is mobilized Diuretics may be indicated during the resolution phase if necessary to combat pulmonary edema.

Pulmonary and Vascular Complications

Serious pulmonary conditions (e g , atelectasis, acute respiratory distress syndrome) have been reported In addition, thromboembolic events both in association with, and separate from, the Ovarian Hyperstimulation Syndrome have been reported following menotropins therapy Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple Pregnancies

Multiple pregnancies have occurred following treatment with Repronex® IM and SC In a clinical trial for ovulation induction in which Repronex® IM and Repronex® SC were directly compared, the rates of multiple pregnancies were as follows Of the four clinical pregnancies with Repronex® IM, two were single and two were multiple pregnancies. Both multiple pregnancies were triplet pregnancies. Of the six clinical pregnancies with Repronex® SC, three were single and three were multiple pregnancies The three multiple pregnancies included one twin pregnancy and two quadruplet pregnancies.

In a clinical trial of IVF patients in which Repronex® IM and Repronex® SC were directly compared, the rates of multiple pregnancies were as follows. Of the 24 continuing pregnancies on

Repronex® IM, 14 were single and 10 were multiple pregnancies. The ten multiple pregnancies included three triplet and seven twin pregnancies. Of the 29 continuing pregnancies on Repronex® SC, 14 were single and 15 were multiple pregnancies. The 15 multiple pregnancies included three quadruplet, three triplet and nine twin pregnancies The patient and her partner should be advised of the potential risk of multiple births before starting treatment

Hypersensitivity/Anaphylactic Reactions
Hypersensitivity/anaphylactic reactions associated with menotropins administration have been reported in some patients. These reactions presented as generalized urticaria, facial edema, angioneurotic edema, and/or dyspnea suggestive of laryngeal edema. The relationship of these symptoms to uncharacterized urinary proteins is uncertain

PRECAUTIONS

General
Careful attention should be given to diagnosis in the selection of candidates for menotropins therapy (see "**INDICATIONS AND USAGE - Selection of Patients**").

Information for Patients
Prior to therapy with Repronex®, patients should be informed of the duration of treatment and the monitoring of their condition that will be required Possible adverse reactions (see **ADVERSE REACTIONS** section) and the risk of multiple births should also be discussed.

Laboratory Tests
Treatment for Induction of ovulation
The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing hCG administration, as well as minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation.

The clinical confirmation of ovulation, is determined by·

a) A rise in basal body temperature,
b) Increase in serum progesterone; and
c) Menstruation following the shift in basal body temperature

When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:

a) Fluid in the cul-de-sac;
b) Ovarian stigmata; and
c) Collapsed follicle

Because of the subjectivity of the various tests for the determination of follicular maturation and ovulation, it cannot be overemphasized that the physician should choose tests with which he/she is thoroughly familiar.

Carcinogenesis and Mutagenesis
Long-term toxicity studies in animals have not been performed to evaluate the carcinogenic potential of menotropins.

Pregnancy
Pregnancy Category X: See **CONTRAINDICATIONS** section

Nursing Mothers
It is not known whether this drug is excreted in human milk Because many drugs are excreted in human milk, caution should be exercised if menotropins are administered to a nursing woman

Pediatric Patients
Safety and effectiveness in pediatric patients have not been established.

Geriatric Patients
Safety and effectiveness in geriatric patients have not been established

ADVERSE REACTIONS

The following adverse reactions, reported during menotropins therapy, are listed in decreasing order of potential severity.

1 Pulmonary and vascular complications (see **WARNINGS**)
2 Ovarian Hyperstimulation Syndrome (see **WARNINGS**)
3 Hemoperitoneum
4 Adnexal torsion (as a complication of ovarian enlargement)
5 Mild to moderate ovarian enlargement
6. Ovarian cysts
7 Abdominal pain
8 Sensitivity to menotropins (Febrile reactions suggestive of allergic response have been reported following the administration of menotropins Reports of flu-like symptoms including fever, chills, musculoskeletal aches, joint pains, nausea, headaches, and malaise have also been reported).
9. Gastrointestinal symptoms (nausea, vomiting, diarrhea, abdominal cramps, bloating)
10. Pain, rash, swelling and/or irritation at the site of injection
11. Body rashes
12. Dizziness, tachycardia, dyspnea, tachypnea

The following medical events have been reported subsequent to pregnancies resulting from menotropins therapy:

1 Ectopic pregnancy
2. Congenital abnormalities

With menotropin therapy congenital abnormalities have been reported. One infant was shown to have multiple congenital anomalies consisting of aplasia of the sigmoid colon, cecovesicle fistula, bifid scrotum, meningocele, bilateral internal tibial torsion, and right metatarsus adductus. Other reported anomalies include imperforate anus, congenital heart lesions, supernumerary digits, hypospadias, extrophy of the bladder, Down's syndrome and hydrocephalus. The incidence of congenital abnormalities does not exceed that found in the general population.

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction, however, a causal relationship has not been established

Adverse events occurring in ≥1% of patients exposed to Repronex® IM or Repronex® SC are described in Table 4.

Table 4: Patients with Adverse Events ≥ 1%

	Repronex® IM (N=101)	Repronex® SC (N=96)
	n (%)	n (%)
Adverse Events		
INJECTION SITE AEs		
Injection Site Edema	1 (1.0)	8 (8.3)*
Injection Site Reaction	2 (2 0)	8 (8.3)*
GENITOURINARY/REPRODUCTIVE AEs		
OHSS	2 (2.0)	5 (5.2)
Vaginal Hemorrhage	8 (7.9)	3 (3.1)
Ovarian Disease	3 (3 0)	8 (8.3)
Ectopic Pregnancy	1 (1.0)	1 (1.0)
Pelvic Pain	3 (3.0)	1 (1.0)
Breast Tenderness	2 (2.0)	2 (2.1)
GASTROINTESTINAL AEs		
Nausea	4 (4.0)	7(7.3)
Vomiting	0 (0)	3 (3.1)
Diarrhea	0 (0)	2(2 1)
Abdominal Cramping	7(6 9)	5(5.2)
Abdominal Pain	5(5 0)	7(7 3)
Enlarged Abdomen	6(6.0)	2 (2.1)
OTHER BODY SYSTEM AEs		
Headache	6 (6.0)	5 (5.2)
Infection	1(1.0)	0 (0)
Dyspnea	1(1 0)	2(2.1)

* Fisher's Exact/Chi-Squared Tests – significant for Repronex® SC vs. Repronex® IM.

DRUG ABUSE AND DEPENDENCE

There have been no reports of abuse or dependence with me

OVERDOSAGE

Aside from possible ovarian hyperstimulation (see **WARNIN** consequences of acute overdosage with menotropins

DOSAGE AND ADMINISTRATION

1. Dosage:
Infertile patients with oligo-anovulation.
The dose of Repronex® to stimulate development of ovarian each patient The lowest dose consistent with achieving good and reported clinical data should be used.

The recommended initial dose of Repronex® for patients wi antagonist pituitary suppression is 150 IU daily for the first 5 monitoring (including serum estradiol levels and vaginal ultr should be adjusted according to individual patient response made more frequently than once every 2 days and should not adjustment The maximum daily dose of Repronex® should no 12 days is not recommended.

If patient response to Repronex® is appropriate, hCG (5000 t 1 day following the last dose of Repronex®. The hCG should greater than 2000 pg/mL, if the ovaries are abnormally enlarg the patient should be advised to refrain from intercourse The of Ovarian Hyperstimulation Syndrome and multiple gestation ly for at least 2 weeks after hCG administration. If there is ina lation without subsequent pregnancy, the course of treatmen The couple should be encouraged to have intercourse daily administration of hCG until ovulation becomes apparent from mination of progestational activity. In the light of the foregoin it should become obvious that, unless a physician is willing patients and be familiar with and conduct the necessary labo Repronex®.

Assisted Reproductive Technologies:
The recommended initial dose of Repronex® for patients w antagonist pituitary suppression is 225 IU. Based on clinical ol levels and vaginal ultrasound results) subsequent dosing s vidual patient response. Adjustments in dose should not be m 2 days and should not exceed more than 75 to 150 IU per a of Repronex® given should not exceed 450 IU and dosing be

Once adequate follicular development is evident, hCG (5 administered to induce final follicular maturation in preparat tration of hCG must be withheld in cases where the ovaries day of therapy. This should reduce the chance of developin

2. Administration:
Dissolve the contents of one to 6 vials of Repronex® **ADMINISTER SUBCUTANEOUSLY OR INTRAMUS** reconstituted material should be discarded.

Parenteral drug products should be inspected visua oration prior to administration, whenever solution and

The lower abdomen (alternating sides) should be us

HOW SUPPLIED

Repronex® (menotropins for injection, USP) is available in via white powder or pellet.

Each vial is available with an accompanying vial of sterile dilu Chloride Injection, USP:

75 IU FSH and 75 IU of LH activity, supplied as.
NDC 55566-7185-1 – Box of 1 vial + 1 vial dilu
NDC 55566-7185-2 – Box of 5 vials + 5 vials d

150 IU FSH and 150 IU of LH activity, supplied as
NDC 55566-7125-1 – Box of 1 vial + 1 vial dilu

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nenotropins Reports of flu-like symptoms including fever,
l pains, nausea, headaches, and malaise have also been

a, vomiting, diarrhea, abdominal cramps, bloating)

in at the site of injection

tachypnea

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established

atients exposed to Repronex® IM or Repronex® SC are

nts with Adverse Events ≥ 1%

	Repronex® IM (N=101) n (%)	Repronex® SC (N=96) n (%)
	1 (1.0)	8 (8.3)*
	2 (2.0)	8 (8.3)*
E AEs		
	2 (2.0)	5 (5.2)
	8 (7.9)	3 (3.1)
	3 (3 0)	8 (8.3)
	1 (1 0)	1 (1.0)
	3 (3 0)	1 (1.0)
	2 (2.0)	2 (2.1)
	4 (4 0)	7(7.3)
	0 (0)	3 (3 1)
	0 (0)	2(2 1)
	7(6.9)	5(5.2)
	5(5.0)	7(7.3)
	6(6.0)	2 (2.1)
	6 (6.0)	5 (5 2)
	1(1.0)	0 (0)
	1(1.0)	2(2.1)

– significant for **Repronex® SC vs. Repronex® IM.**

DRUG ABUSE AND DEPENDENCE
There have been no reports of abuse or dependence with menotropins.

OVERDOSAGE
Aside from possible ovarian hyperstimulation (see **WARNINGS**), little is known concerning the consequences of acute overdosage with menotropins.

DOSAGE AND ADMINISTRATION

1. Dosage:

Infertile patients with oligo-anovulation:
The dose of Repronex® to stimulate development of ovarian follicles must be individualized for each patient. The lowest dose consistent with achieving good results based on clinical experience and reported clinical data should be used

The recommended initial dose of Repronex® for patients who have received GnRH agonist or antagonist pituitary suppression is 150 IU daily for the first 5 days of treatment Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Repronex® should not exceed 450 IU and dosing beyond 12 days is not recommended.

If patient response to Repronex® is appropriate, hCG (5000 to 10,000 USP units) should be given 1 day following the last dose of Repronex® The hCG should be withheld if the serum estradiol is greater than 2000 pg/mL, if the ovaries are abnormally enlarged or if abdominal pain occurs, and the patient should be advised to refrain from intercourse. These precautions may reduce the risk of Ovarian Hyperstimulation Syndrome and multiple gestation. Patients should be followed closely for at least 2 weeks after hCG administration. If there is inadequate follicle development or ovulation without subsequent pregnancy, the course of treatment with Repronex® may be repeated The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational activity In the light of the foregoing indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Repronex®.

Assisted Reproductive Technologies:
The recommended initial dose of Repronex® for patients who have received GnRH agonist or antagonist pituitary suppression is 225 IU Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Repronex® given should not exceed 450 IU and dosing beyond 12 days is not recommended

Once adequate follicular development is evident, hCG (5000 – 10,000 USP units) should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing OHSS

2. Administration:
Dissolve the contents of one to 6 vials of Repronex® in one to two mL of sterile saline and **ADMINISTER SUBCUTANEOUSLY OR INTRAMUSCULARLY** immediately Any unused reconstituted material should be discarded.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit

The lower abdomen (alternating sides) should be used for subcutaneous administration.

HOW SUPPLIED
Repronex® (menotropins for injection, USP) is available in vials as a sterile, lyophilized, white to off-white powder or pellet.

Each vial is available with an accompanying vial of sterile diluent containing 2 mL of 0 9% Sodium Chloride Injection, USP:

75 IU FSH and 75 IU of LH activity, supplied as:
NDC 55566-7185-1 – Box of 1 vial + 1 vial diluent.
NDC 55566-7185-2 – Box of 5 vials + 5 vials diluent

150 IU FSH and 150 IU of LH activity, supplied as:
NDC 55566-7125-1 – Box of 1 vial + 1 vial diluent.

By biological assay, one IU of LH for the Second International Reference Preparation (2nd-IRP) for hMG is biologically equivalent to approximately 0 5 U of hCG.

Lyophilized powder may be stored refrigerated or at room temperature (3° to 25°C/37° to 77°F) Protect from light Use immediately after reconstitution Discard unused material.

℞ only

Vials of sterile diluent of 0 9% Sodium Chloride Injection, USP manufactured for Ferring Pharmaceuticals Inc.

Manufactured for
FERRING PHARMACEUTICALS INC
TARRYTOWN, NY 10591
By: LEDERLE PARENTERALS, INC
Carolina, Puerto Rico 00987
CI 6098-1
6039-01
8/99