CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21047

CORRESPONDENCE

FERRING
PHARMACEUTICALS

ONE AMENDMENT

August 19, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21,047 - Repronex®

Dear Dr. Rarick:

Please find enclosed an Amendment to the Repronex® NDA #21,047. The following items are included in this Amendment:

- Revised Text Version – Package Insert
- Final Text Version – Package Insert
- Carton Labeling – Repronex 75 IU – Single Vial
- Carton Labeling – Repronex 150 IU – Single Vial
- Vial Labeling – Repronex 150 IU – Single Vial

If you have any additional questions, please contact me at 914-333-8932 with any questions.

Sincerely,

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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
AUG 20 1999
HFD-580

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

FERRING
PHARMACEUTICALS

August 13, 1999

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Repronex NDA 21,047 – Safety Update

Dear Dr. Rarick:

The only clinical studies of Repronex which have been sponsored by Ferring are 97-01 (OI) and 97-02 (IVF), both completed. There are no ongoing clinical studies with Repronex.

No spontaneous adverse events have been reported within the last year.

Sincerely.

Stephanie Tam for
Ron Nardi

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

RVN:mkv

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

US

FERRING

PHARMACEUTICALS

August 12, 1999

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Repronex NDA 21,047

Dear Dr. Rarick:

Attached please find an amendment to the above referenced NDA #21,047 for Repronex. This amendment contains:

- Proposed Package Insert for Repronex reflecting changes discussed with FDA.
- Proposed Text for the Carton and Primary Vial Labels reflecting changes discussed with FDA.
- Birth Data (follow up data not available for patients) requested by FDA
- Patent Certification according to CFR 314.54

Please note that we are requesting exclusivity for Repronex consistent with the exclusivity for NDAs containing significant clinical studies sponsored by the applicant. We also request a waiver of the pediatric study requirement since this product should not be used in a pediatric population.

For your reference we also include the cover letter relating to the safety studies submitted to the ANDA 73-598/599. These data are referenced in this NDA (#21,047). The information is supplied to facilitate locating the data in the ANDA file. A deskcopy of the ANDA amendment is enclosed for your convenience.

Please feel free to contact me at 914-333-8932 with any questions.

Sincerely,

Wayne C. Anderson for
Ron Nardi

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

RVN:mgc
Enclosures

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

US

ORIGINAL

ORIG AMENDMENT

BL

FERRING

PHARMACEUTICALS

August 9, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive & Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Repronex NDA 21047 - DRAFT Labeling Amendment

Dear Dr. Rarick:

Enclosed please find the revised text version of the package insert for Repronex. This version represents changes in the Dosage and Administration section (pages 16 and 17) to conform with your request that the wording be specific to our Repronex clinical studies. Please note we have bracketed a small portion of the text on pages 11 and 12 for your comments. This text lists somewhat our of date tests for monitoring response to menotropin therapy. We are prepared to delete this text if agreeable to FDA.

We will await your comments on this version of the package insert and provide finalized text thereafter.

Sincerely,

FOR RN

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

RVN/mgc

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ [illegible]

CSO 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

US

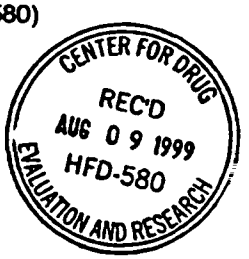
ORIGINAL

ORIG AMENDMENT
62

FERRING
PHARMACEUTICALS

August 6, 1999

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: REPRONEX ®, NDA# 21, 047

Dear Dr. Rarick:

Enclosed please find the revised package label for Repronex. This version differs from the one faxed on Tuesday, August 3, 1999 in reversing the order of the routes of administration (subcutaneous now precedes intramuscular) Please note we have bracketed a small portion of the text on pages 11 and 12 for your comments. This text lists somewhat out of date tests for monitoring response to menotropin therapy. We are prepared to delete this if agreeable to FDA.

We will await your comments on this version of the package label and provide finalized text thereafter.

Sincerely,

FOR RN

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

RN: jac

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

US

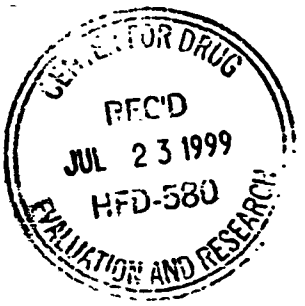
FERRING

PHARMACEUTICALS

NEW CORRESP

NC

July 22, 1999



Diane Moore
Division of Reproductive and Urologic Drugs
US Food and Drug Administration
HFD-580, Room 17B45
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21, 047

Dear Ms. Moore:

As per your request, enclosed please find a copy of Volume 2A of the Repronex™ submission that includes all pages previously missing.

I hope this satisfies your request. If you require any further assistance, please contact me at 913-333-8933 or by fax at 914-631-5120. if you require any further assistance.

Sincerely,

Jody Ann Carlucci

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

CC: Ronald V. Nardi, Ph.D.
Michele Cobham

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

US

FERRING

PHARMACEUTICALS

July 22, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21,047 - Repronex®

Dear Dr. Rarick:

Enclosed please find 4 copies of the DRAFT text versions of our Carton Labeling and Vial Label for Repronex®.

Please contact me at 914-333-8932 with any questions.

Sincerely,

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

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

US

ORIGINAL

ORIG AMENDMENT

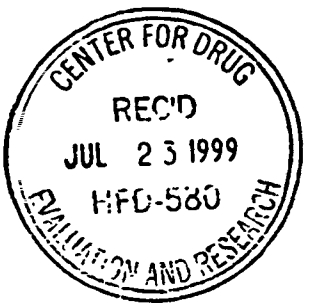
BM

FERRING

PHARMACEUTICALS

July 22, 1999

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: REPRONEX ®, NDA# 21, 047

Dear Dr. Rarick:

Attached please find an amendment correcting numerical discrepancies in the above referenced NDA.

Per Diane Moore's discussion with Dr. Fein, the Adverse Event Tables do contain numerical errors which we have corrected in the tables below. The discrepancies were arithmetic errors in tallying the total numbers of patients by treatment group. Three hundred ninety four is the correct total with 101 patients receiving Repronex IM, 196 receiving Repronex SC and 97 receiving Pergonal IM.

Patients with Adverse Events

Parameter	**Repronex IM N=101**	**Repronex SC N=196 ***	**Pergonal IM N=97**
AE of any type (%)	34 (33.7)	39(20.0)	35(36.0)
Serious AE (%)	2(2.0)	4(2.0)†	5(5.1)

* Includes 100 open label patients from Study Meno 96/01 NL (IVF)
† Includes 2 cases of OHSS from Study Meno 96/01 NL (IVF)

Incidence of Adverse Events

Parameter	**Repronex IM N=101**	**Repronex SC N=196 ***	**Pergonal IM N=97**
All AEs	85	104	72
Serious AEs	2	4†	5

* Includes 100 open label patients from Study Meno 96/01 NL (IVF)
† Includes 2 cases of OHSS from Study Meno 96/01 NL (IVF)

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

We apologize for the error and regret any confusion or inconvenience to your staff. Please contact me at 914-333-8932 if you require any further assistance.

Sincerely,

Ronald V. Nardi

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

RN: jac

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I ☐ MEMO

CSO INITIALS DATE

US

ORIGINAL

ORIG AMENDMENT

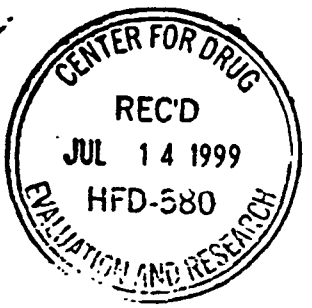
BL

FERRING

PHARMACEUTICALS

July 12, 1999

Lisa Rarrick, MD
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



RE: NDA 21047, Labeling Amendment

Dear Dr. Rarrick:

Pursuant to the question raised by Diane Moore concerning multiple pregnancy rates for the Repronex Package Insert, attached please find the tables supporting the Package Insert information.

The multiple gestation incidence for ovulation induction which is described in the Labeling Amendment dated June 17, 1999 on page 10 under multiple births was calculated based on Table 10, page 41 in Volume 8H of the Repronex NDA.

For each treatment group, Repronex IM, Repronex SC and Pergonal IM the numerator was the number of patients with multiple gestations (twins, triplets, and quadruplets) and the denominator was the number of patients who ovulated. Therefore, the percentages as stated in the Labeling Amendment were 2/23 (8.7%) for Repronex IM, 3/25 (12%) for Repronex SC and 5/21 (23.8%) for Pergonal IM.

I hope this satisfies the request. If there is any further information you require, please do not hesitate to contact me at 914-333-8947.

Thank you for your attention to this matter.

Sincerely,

for RN

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

RN: jac

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO 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

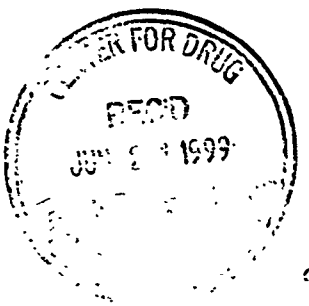
ORIGINAL

ORIG AMENDMENT

FERRING
PHARMACEUTICALS

June 18, 1999 BB

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Noted
6/23/99
JL
Also got
orange jacket
to review

RE: NDA 21,047 - Repronex™

Dear Dr. Rarick:

Enclosed is the information FDA requested concerning standard curves and raw counts for FSH and LH assays from Study FPI Rep 97-01 which prepared. We submit this amendment to NDA #21,047 in triplicate.

Please note that the NDA amendment dated March 1999 contains an error. Volume 6C is Appendix A related to the normal volunteer Menogon PK study. Volume 6D is Appendix B related to the FPI Rep 97-01 study. This amendment is Volume 6F related to the FPI Rep 97-01 study.

Please contact us at 914-333-8932 with any questions.

Sincerely,

Ronald V. Nardi

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

RVN/mgc

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO 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

ORIGINAL

ORIG AMENDMENT

FERRING
PHARMACEUTICALS

June 17, 1999

Lisa Rarick, M.D.
Director, Division of Reproductive
& Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 21,047 - Repronex™

Dear Dr. Rarick:

Please find enclosed a labeling amendment, for the package insert, to the labeling submitted under the original NDA submission for Repronex, NDA 21,047. This amendment consists of an:

- FDA form 356H
- Package Insert Labeling – Corrected Version (showing revisions made)
- Package Insert Labeling – Final Text Version

I look forward to hearing from you soon.

Sincerely,

Ronald V. Nardi

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

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

US

FERRING
PHARMACEUTICALS

ORIGINAL

ORIG AMENDMENT

BC

May 11, 1999

Noted
5/14/99
JLB

Ms. Diane Moore
Division of Reproductive and Urologic Drugs
US Food and Drug Administration
HFD-580, Room 17B45
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

reviewed and communicated with Dr. Nardi of Ferring Pharmaceuticals via T con on 5/14/99 2:30p - other present A. Powell and D. Spoler

RE: Repronex™ NDA #21047

Dear Ms. Moore:

In response to your request for assay method validation reports concerning FSH and LH, the following information provided by the is submitted:

- ◊ Follicle Stimulating Hormone (FSH) on the ACS:180
- ◊ Luteinizing Hormone (LH2) on ACS:180 Immunoassay Analyzer

Thank you for your time. If there is any further information you require, please contact me at 914-333-8933.

Sincerely,

Jody Ann Carlucci

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Enclosures: 3 Sets of Review Material

CC: Ronald V. Nardi, Ph.D.
Michele Cobham

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

US

ORIGINAL

FERRING

PHARMACEUTICALS

March 24, 1999

ORIG AMENDMENT

SV

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA # 21,047
IND Repronex™ (menotropins for injection, USP)
ANDA #73-598, ANDA # 73-599

Dear Dr. Rarick,

Enclosed please find an amendment to NDA #21,047. This amendment contains the safety update information required for pending applications and additional data demonstrating the safety and efficacy of the subcutaneous route of administration for Repronex. Repronex is approved and marketed under the above referenced ANDAs in which intramuscular administration is the approved route administration.

NDA #21,047 seeks the approval of a new route of administration based on data from clinical trials in the United States and Europe. Controlled trials in the US compared Repronex administered via a subcutaneous route to Repronex administered via an intramuscular route and Pergonal administered via an intramuscular route. This amendment contains:

- the final clinical report on the recently completed ovulation induction study for which an interim report was submitted previously;
- the final pharmacokinetic analyses and report which were part of the ovulation induction study;
- the reanalysis of the single-dose pharmacokinetic study requested by the Biopharmaceutics Division at the FDA;
- modification of the proposed labeling to reflect the additional information.

The safety and efficacy data from the ovulation induction study and the studies of patients undergoing *in vitro* fertilization demonstrated that subcutaneous administration of Repronex:

- was pharmacologically equivalent to intramuscular administration of Repronex and Pergonal
- was at least therapeutically equivalent to intramuscular administration of Repronex and Pergonal
- had a benefit/risk ratio similar to intramuscular administration of either Repronex or Pergonal.

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

Pharmacokinetic data, from European and US studies, presented in Section 6 demonstrate pharmacokinetic profiles consistent with the literature for the different routes of administration.

Please note that this amendment contains a total of 24 volumes. Volume numbers correspond to each of the Sections of the NDA (i.e.1-15). Volumes in this amendment continue the numerical/alphabetical sequence in that, if a Section required more than one volume, the set of volumes is identified further with letters in alphabetical sequence (e.g. Volumes 8a, 8b, etc. correspond to Section 8 items). Individual reviewing disciplines have appropriately color-coded volumes including a Summary volume (Section 2) and a Labeling volume (Section 4).

We acknowledge the continuing requirement for periodic updates during the review of this application. If you need any other information please feel free to contact me at 914-333-8932 or by fax at 914-631-5120. If you have specific questions concerning the clinical data you may also contact Dr. Seymour Fein at 914-333-8947 or by fax at 914-631-5120.

Sincerely,

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

Enclosures: amendment for NDA #21,047

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

US

FERRING
PHARMACEUTICALS

October 26, 1998

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug [illegible]s (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA # 21,047
IND [illegible] Repronex™ (menotropins for injection, USP)
ANDA #73-598, ANDA # 73-599

Dear Dr. Rarick,

Enclosed please find NDA #21,047, which is respectfully submitted, for your review as a 505 (b)(2) application. Repronex is approved and marketed under the above referenced ANDAs in which intramuscular administration is the approved route administration. The data contained in this application demonstrate that subcutaneous administration of Repronex is also safe and effective in the previously approved indications.

This application seeks the approval of a new route of administration based on data from clinical trials in the United States and Europe. Controlled trials in the US compared Repronex administered via a subcutaneous route to Repronex administered via an intramuscular route and Pergonal administered via an intramuscular route. The studies were parallel group, randomized, open-label trials. The study in the *in vitro* fertilization patients is complete and demonstrated that subcutaneous administration of Repronex:

- was pharmacologically equivalent to intramuscular administration of Repronex and Pergonal
- was at least therapeutically equivalent to intramuscular administration of Repronex and Pergonal
- had a benefit/risk ratio similar to intramuscular administration of either Repronex or Pergonal.

An interim report of the on-going ovulation induction protocol in the US is included. The interim safety assessment demonstrates that subcutaneous administration is safe and well-tolerated in this population of patients. An open-label European study in patients undergoing *in vitro* fertilization demonstrates that subcutaneous administration of Menogon, the European trademark for Ferring's brand of menotropins, is safe and effective.

Pharmacokinetic data from European and US studies are presented in Section 6. These data are descriptive. They were not intended to demonstrate bioequivalence of the different routes of administration. They do demonstrate pharmacokinetic profiles consistent with the literature for the different routes of administration.

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

Sincerely,

/S/ 12/30/98

Lana L. Pauls, M.P.H.
Acting Associate Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-047
HFD-580/Div. Files
HFD-580/D.Moore
HFD-580/LRarick/MMann/SSlaughter/RBennett/MRhee
HFD-580/KRaheja/AJordan/JLau/AParekh/LKammerman
HFD-510/MHaber
DISTRICT OFFICE

Drafted by: dm/December 21, 1998

Concurrence:
TRumble 12.28.98

/S/ 12/28/98

filename: N21047AK.DOC

ACKNOWLEDGEMENT (AC)

NDA 21-047

DEC 28 1998

Ferring Pharmaceuticals, Inc.
Attention: Ronald V. Nardi, Ph.D.
Vice President, Regulatory and Scientific Affairs
120 White Plains Road, Suite 400
Tarrytown, NY 10591

Dear Dr. Nardi:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Repronex (menotropins for injection), USP 75 IU FSH and 75 IU of LH activity and 150 IU FSH and 150 IU of LH activity
Therapeutic Classification:	Standard (S)
Date of Application:	October 26, 1998
Date of Receipt:	October 28, 1998
Our Reference Number:	21-047

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 27, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 28, 1999, and the secondary user fee goal date will be October 28, 1999.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Please note that the application contains a total of 29 volumes. Volume numbers correspond to each of the Sections of the NDA (i.e.1-15). If a Section required more than one volume the set of volumes is identified further with letters in alphabetical sequence (e.g. Volumes 8a, 8b, etc. correspond to Section 8 items). Individual reviewing disciplines have appropriately color-coded volumes including a Summary volume (Section 2) and a Labeling volume (Section 4). Each page of the original has a unique two-part page number that includes both the volume number and page number within that volume (e.g. Vol. 8a page 010).

Attached please find a copy of a letter from granting the right of reference to DMF A User Fee Cover Sheet with a cover letter is also attached. User fee payments will be made using user fee

We acknowledge the requirement for periodic updates during the review of this application. If you need any other information please feel free to contact me at 914-333-8932 or by fax at 914-631-5120. If you have specific questions concerning the clinical data you may also contact Dr. Seymour Fein at 914-333-8947 or by fax at 914-631-5120.

Sincerely,

Ronald V. Nardi

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

Enclosures: NDA #21,047
Attachments: User Fee Cover sheet
Copy of Right of Reference – Instituto Massone