CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-484

Correspondence

US

FERRING
PHARMACEUTICALS

ORIGINAL

November 27, 2002

RECEIVED
DEC 0 2 2002
FDR/CDER

RL
ORIG AMENDMENT

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

Attn: Central Document Room

Re: NDA 21-484, Bravelle™ (urofollitropin for injection)
S-005, Resubmission of Electronic Files

Dear Dr. Shames:

In the electronic portion of our Amendment 004 (November 26, 2002) to this NDA we inadvertently omitted several files from the floppy disks (cover letter, FDA form 356h and table of contents). The revised proposed package insert was present in both Word and PDF format. In this amendment we are resubmitting the electronic files (floppy disk), including the files that were inadvertently omitted in amendment 004.

Thank you for your assistance in this matter.

Sincerely,

MBernhard

Michael I. Bernhard, Ph.D.
Senior Director, Regulatory Affairs

RECEIVED
NOV 2 7 2002
OGD / CDER

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

N.000 BL

ORIG AMENDMENT

FERRING
PHARMACEUTICALS

November 26, 2002

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

RECEIVED
DEC 0 2 2002
MEGA/CDER

RECEIVED
DEC 0 3 2002
FDR/CDER

Re: NDA 21-484, Bravelle™ (urofollitropin for injection)
S-004, Labeling Correction

Dear Dr. Shames:

Ferring Pharmaceuticals is submitting a labeling amendment to NDA 21-484. The process for this amendment was agreed upon with Ms. Archana Reddy, Project Manager. in conversations with Dr. Michael Bernhard, Senior Director of Regulatory Affairs, on November 22, 2002.

As discussed during your meeting with Dr. Kenneth Kashkin, Vice President of Medical and Regulatory Affairs, on November 21, 2002, the data for one patient in study FPI FSH 99-03 was incorrectly assigned to the Bravelle™ SC cohort instead of the Follistim® SC cohort because the investigator mistakenly treated with Follistim instead of Bravelle SC. This was reported as a protocol violation in the NDA. Tabulations in the package insert did not reflect the corrected assignment. This patient was treated with Follistim®. received hCG, did not become pregnant and experienced no adverse events.

This amendment consists of the following changes to the package insert that was submitted on July 19, 2002:

- Corrections resulting from incorrectly assigned patient:
  - Pages 4 and 6: 72 of the oligo-anovulatory patients were treated with Bravelle;
  - Page 4, Table № 5: 35 patients were treated with Bravelle SC and this resulted in a change in the denominator and the calculated percentages reported in the Bravelle column of this table.
  - Page 9: the safety studies enrolled 281 patients treated with Bravelle. including 72 for ovulation induction and 209 for IVF.
  - Page 10, Table № 8: The numbers in the Bravelle SC column are corrected to a total of 35 patients.

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

- Additional Corrections
  - Page 4: Transcription error in Table № 4, "Recipients" column, should read N=30; this also resulted in revised percent calculations.
  - Page 7: Deletion of columns containing Follistim® data from Tables № 6 and 7, in previous amendments to this NDA and NDA № 21-289 resulted in changes to the total number of patients listed in these tables. The total number of patients is corrected in the accompanying text to 209 patients undergoing ART (Table № 6) and 72 patients undergoing ovulation induction (Table № 7).
  - Table № 4 of the ovulation induction NDA (NDA № 21-289) was revised, at the Division's request, on April 30, 2002 to include all adverse events occurring in ≥ 2% of patients and this table was incorporated in NDA № 21-484 as Table № 8. Although the title of the table was revised, the data listings were not updated. We have taken this opportunity to update the data listing in this table. As even one adverse event constitutes more than 2% of the test population, all adverse events are now listed in this table.
  - Page 11, Table № 9: This table is revised to include adverse events occurring in ≥ 2% of the patients that were not previously included in the table.
  - We have updated our address to our new location (effective December 6, 2002).

These revisions do not result in any substantive changes to the efficacy or safety evaluations or overall conclusions.

Sincerely,

MBernhard

Michael I. Bernhard, Ph.D.
Senior Director, Regulatory Affairs

US

FERRING
PHARMACEUTICALS

November 15, 2002

ORIGINAL

RECEIVED
NOV 26 2002
FDR/CDER

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

Re: NDA 21-484, Bravelle™ (urofollitropin for injection)
Change of Address

Dear Dr. Shames:

On December 6, 2002 we are moving to a new address:

Ferring Pharmaceuticals, Inc.
400 Rella Boulevard
Suite 300
Suffern, New York 10901

Our telephone number is 888-793-6367.

Please adjust your records accordingly.

Sincerely,

Michael I. Bernhard, Ph.D.
Senior Director, Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-484

Ferring Pharmaceuticals, Inc.
Attention: Ronald Nardi, Ph.D.
Executive Vice President, Research and Development
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:	Bravelle™ (purified urofollitropin)
Review Priority Classification:	Standard (S)
Date of Application:	February 15, 2002
Date of Receipt:	February 19, 2002
Our Reference Number:	NDA 21-484

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 April 19, 2002, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be December 19, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the

application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

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

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

{See appended electronic signature page}

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

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

/s/

Diane V. Moore
2/25/02 05:23:34 PM
for Terri Rumble

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 29

Sam Najmabadi, M.D.
Center for Reproductive Health & Gynecology
23861 McBean Parkway, Suite C-6
Valencia, California 91355

Dear Dr. Najmabadi:

Between July 31 and August 8, 2002, Mr. Ronald L. Koller, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #FPI FSH 2001-01 entitled: "A Randomized, Assessor Blind, Parallel Group, Multicenter, Efficacy Study Comparing Purified FSH (Bravelle™) SC and Follistim® SC, in Female Patients Undergoing In Vitro Fertilization (IVF)") of the investigational drug Bravelle™ (purified FSH), performed for Ferring Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to ensure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Koller presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We note your August 16, 2002 response and wish to emphasize the following:

1. You did not adhere to the investigational plan, which required subjects to be seropositive for rubella and varicella within 90 days prior to leuprolide acetate treatment, as required by 21 CFR 312.60. Specifically:

   a. Subject 006 was antibody titer negative for varicella;

   b. Subject 008 was antibody titer negative for rubella; and

   c. Subject 009 was not tested for rubella immunity.

2. The consent form did not contain a description of any reasonably foreseeable risks or discomforts as required by 21 CFR 50.25(a) in that it did not state the risks/side effects from the combined use of leuprolide acetate and progesterone.

Please make appropriate corrections/changes in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Koller during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, by letter, at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

CFN: 3003748150
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_____2)VAI- no response required
__X___3)VAI-rr, response received
_____4)OAI

Deficiencies noted:
__X__inadequate informed consent form (03)
__X__failure to adhere to protocol (05)
Deficiency Codes: 3, 5

cc:
HFA-224
HFD-580 Doc.Rm. NDA#21-484
HFD-580 Review Div.Dir./Shames
HFD-580 MO/Bennett
HFD-580 PM/Reddy
HFD-46/47c/r/s/ GCP File #10688
HFD-46/47 GCP Reviewer/Blay
HFD-46/47 CSO/Slavin
HFR-PA252 DIB/Stokke
HFR- PA2565 Bimo/Field Investigator/Koller
r/d: (AS):9/10/02
reviewed:aeh:9/11/02
f/t:**ml:9/12/02:sg:11/20/02**

o:\slavin\Najmabadi letter

Reviewer Note to Rev. Div. M.O.
This was a routine pre-approval inspection. The site screened 15 subjects and enrolled 12 subjects. Eleven subjects received the investigational drug. One subject was withdrawn due to an ovarian cyst. There were no deaths or SAE's reported at this site. The audit verified written informed consent was obtained from all subjects. The investigator audited all subjects' records. Case report forms were compared to source documents and sponsor data listings. No discrepancies were noted. A Form 483 was issued pertaining to violations of inclusion criteria for 3 subjects. The investigator submitted a written response to the 483 acknowledging the errors. In addition, it was noted that the consent form did not state the potential risks/side effects of leuprolide and progesterone. The data appear acceptable in support of the license application. Inspection is classified as VAI-rr.

July 25, 2002

ORIGINAL

FERRING
PHARMACEUTICALS

Daniel Shames, 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 Fisher Lane
Rockville, MD 20857

ORIG AMENDMENT

RECEIVED Aug 1, 2002
JUL 30 2002
HFD-580/CDER

RE: Bravelle™ - NDA #21-484

BB

Dear Dr. Shames:

Ferring is responding to the request from Biopharmaceutics for the 90% confidence intervals for Cmax and AUC for Bravelle™ administered SC and IM.

The FPI FSH 99-02 study was a single and multiple dose PK trial in normal female subjects. The SC and IM routes were evaluated in separate cohorts of subjects to establish the PK profiles of each route. Based on PK data from Repronex® and other gonadotropins, Ferring did not expect the SC and IM routes to be bioequivalent and did not design the FPI FSH 99-02 study to attempt to demonstrate this which would have required a cross-over design. The PK data from the FPI FSH 99-02 trial, as expected, do not support the biopharmaceutical equivalence of the SC and IM routes for Bravelle™.

Ferring restates its position, however, that the pharmacological and therapeutic equivalence of SC and IM Bravelle™ has been established for the ovulation induction indication in study FPI FSH 99-03 and for the IVF indication in study FPI FSH 99-04. In addition, the non-inferiority of Bravelle™ given both SC and IM to the active comparator, Follistim® for IVF was statistically proven in the FPI FH 99-04 study. The repeat IVF study, 2001-01 confirms these results for the SC route and, therefore provides additional documentation to support the FDA's approval of the IVF indication for both SC and IM administration.

Please contact me at 914-333-8932 if you have any additional questions.

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

Sincerely,

Stephanie Adam (for RVN)

Ronald V. Nardi, Ph.D.
Executive Vice President, Research & Development

cc to: A. Rheddy, Project Manager, FDA

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

DUPLICATE

FERRING
PHARMACEUTICALS

July 19, 2002

ORIG AMENDMENT

RECEIVED
JUL 2 2 2002
HFD-580/CDER

Daniel Shames, 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 Fisher Lane
Rockville, MD 20857

N-000-154

RE: Bravelle™ - NDA #21-484, Amendment # S002

Dear Dr. Shames:

Ferring is submitting this amendment to its administrative NDA 21-484 for Bravelle™ as treatment for infertile women undergoing *in vitro* fertilization. The submission consists of revised package labeling in both paper and electronic formats. The package insert has been updated to reflect the exact text and format which FDA approved for the Bravelle™ NDA #21,289 in all sections common to the two labels. In addition, all nomenclature and tabular formats for the 21-484 package label have been made consistent with the approved 21,289 label. There are no changes or new clinical data compared to the previous version of the 21-484 label. The revised format version of the package label is provided in color for ease of review. In addition, a final clean version is provide in black and white paper and in electronic format both as a MSWord document and adobe acrobat .pdf files on diskette.

Also included in this submission are paper and electronic copies of the final, printed carton and vial labels which are currently in use for the Bravelle™ product being commercially distributed under approved NDA 21,289. There are no changes to the carton and vial labels for NDA 21-484.

Please contact me at 914-333-8932 if you have any additional questions.

Sincerely,

Seymour Stein

Ronald V. Nardi, Ph.D.
Executive Vice President, Research & Development

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

NDA ORIG AMENDMENT

RECEIVED
MAY 0 2 2002
HFD-580/CDER

May 1, 2002

Daniel Shames, M.D.
Acting 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 Fisher Lane
Rockville, MD 20857

N-000-15 M1

RE: NDA 21,484/S001

Dear Dr. Shames:

Ferring is submitting this amendment to its Bravelle™ NDA 21,289. It consists of a regulatory appeals letter concerning your Division's review and treatment of the clinical studies in support of the IVF indication (99-04 and 2001-01). This letter has been sent directly to your office by our legal counsel and is being filed to this NDA and separately to NDA 21,289 and IND

Please contact me at (914) 333-8932 or (914) 333-8935 with any questions.

Sincerely,

Stephanie Lee (for RVN)
Ronald V. Nardi, Ph.D.
Executive Vice President, Research & Development

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

US

FERRING
PHARMACEUTICALS

February 15, 2002

Daniel Shames, MD
Acting Director
Division of Reproductive and Urologic Drug Products (HFD-5480)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
FOOD AND DRUG ADMINISTRATION
5600 Fisher Lane
Rockville, MD 20857

RE: Bravelle™ NDA 21-484 – Original NDA Submission

Dear Dr. Shames:

Ferring is submitting, at the direction of your Division, an Administrative NDA (NDA #21-484) for the Assisted Reproductive Technologies (ART/IVF) clinical indication for our purified urofollitropin drug, Bravelle™. The project management staff at the Division of Reproductive and Urologic Drug Products has informed us that this administrative NDA, referenced to NDA #21-289 is exempt from User Fees.

The NDA consists of the following components:

- A Final Study Report for the repeat IVF study, FPI FSH 2001-01, which was assessor-blinded and in compliance with the analytical plan requirements specified by FDA (Volume 8).
- A final study report for IVF study FPI FSH 99-04 with a revised statistical report.
- A final study report for IVF donor egg study FPI FSH 99-05
- Revised Package Labeling – Package Insert (Volumes 2 and 3)
- Updated Integrated Summary of Safety including 2001-01 (Volumes 3, 8, and 9)
- Updated Integrated Summary of Efficacy including 2001-01 (Volume 8)
- Statistical Report, Tables and Data Listings for FPI FSH 2001-01 (Volumes 8, 9, 10 and 11)
- Case Report Form Printouts for Serious AEs (Volume 12)

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

- Appropriate references to NDA #21-289 for CMC (Volume 4), Pharm/Tox (Volume 5), Biopharmaceutics (Volume 6), Microbiology (volume 7) and Miscellaneous Administrative issues (Volumes 13-19 which are located in Volume 1)

The FPI FSH 2001-01 study achieved unusually tight standard deviations and 95% confidence intervals (-2.1) for the primary efficacy variable of mean oocytes retrieved compared to the active control reference standard. With the submission of this study report, Ferring has fully and adequately responded to the clinical/statistical deficiency for the IVF indication as stated in the Not Approvable Letter of July 2001.

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

Sincerely,

Ronald V. Nardi, Ph.D.
Executive Vice President,
Research & Development

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-484

INFORMATION REQUEST LETTER

Ferring Pharmaceuticals, Inc.
Attention: Michael Bernhard, Ph.D.
Senior Director, Regulatory Affairs
120 White Plains Road
Suite 400
Tarrytown, NY 10591

Dear Dr. Bernhard:

Please refer to your February 15, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bravelle™ (urofollitropin for injection purified).

We also refer to your submissions dated July 19, 2002 and November 26, 2002.

We are reviewing the Labeling section of your February 15, 2002 submission and have the following attached labeling comments. We request a prompt written response to the attached labeling comments in order to continue our evaluation of your NDA.

If you have any questions, call Archana Reddy, M.P.H., Regulatory Project Manager, at 301- 827 – 4260.

Sincerely,

{See appended electronic signature page}

/S/

Daniel Shames, M.D.
Division Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Cc: Enclosure

22

_____ pages redacted from this section of the approval package consisted of draft labeling

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

/s/

Daniel A. Shames
12/13/02 02:05:15 PM