CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-289

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-289

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

Dear Dr. Nardi:

Please refer to your new drug application (NDA) dated September 28, 2001, received September 29, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Bravelle (urofollitropin for injection, purified) subcutaneous or intramuscular injection.

We acknowledge receipt of your submissions dated February 9 and 15, March 1, April 3, 5, 20, 23 and 25, May 1, 14, 15 and 24, June 8, 14, 27 and 29, July 5 and 11, 2001.

We also refer to your chemistry submissions dated July 11 and 19, 2001. These submissions have not been reviewed in the current review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Facilities:

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the investigator.

The following information is needed to address the deficiency:

Satisfactory inspections of all manufacturing and packaging facilities for this product will be required before this application may be approved.

Chemistry:

1. Insufficient information was provided to assure the identity, strength, quality and purity of the drug substance and the drug product.

2. The proposed expiration date of [redacted] is not acceptable.

The following information is needed to address the deficiency:

1. Provide characterization of the [redacted] of the drug substance with better defined [redacted] technique to demonstrate clear distribution of [redacted] within a defined [redacted]

2. Provide updated specifications to assure consistent quality of the drug substance, including specification for [redacted]

   detection methods. A valid procedure is also required by which an in-house reference standard can be established from an international standard.

3. Justify, with data, the [redacted] in the manufacture of the drug product.

4. Provide chemistry, manufacturing, and controls information for the 0.9% sodium chloride solution diluent. Cross referencing to a DMF will suffice.

5. Provide specifications for the drug product including specifications for monomer (intact protein molecule) content by [redacted]

6. Submit three copies of complete Methods Validation package for validation by Agency's laboratories.

7. Submit a single, unified stability protocol, and corresponding stability data to evaluate the expiration date of the drug product.

Clinical:

Based on the original statistical analysis plan, neither the subcutaneously administered Bravelle™ nor the intramuscularly administered Bravelle™ demonstrated non-inferiority to subcutaneously administered Follistim® for the proposed indication of multiple follicular development for use in Assisted Reproductive Technology (ART).

The following information is needed to address this deficiency:

Conduct a new trial to demonstrate the safety and efficacy of Bravelle™ for multiple follicular development in ART. Ideally, this trial should be a blinded comparative trial using an approved active comparator to demonstrate that Bravelle™ is both clinically and statistically non-inferior to the active comparator for the proposed indication of multiple follicular development.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Susan Allen
7/27/01 03:58:39 PM

APPEARS THIS WAY
ON ORIGINAL

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-289 /SE_____ - _____

Drug Bravelle (follitropin beta for inj) Applicant _____

RPM DeGuia/Spell-Lesane/Rumble Phone (301) 827-4260

X 505(b)(1)
☐505(b)(2) Reference listed drug: Follistim (follitropin beta for injection) NDA-20-582

☐Fast Track ☐Rolling Review Review priority: ☒ S ☐P

Pivotal IND(s) _____

Application classifications:
Chem Class 3S
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary _____
Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: ☒ User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... ☐AP ☐ AE ☒ NA

- Labeling & Labels
  - FDA revised labeling and reviews..... N/A
  - Original proposed labeling (package insert, patient package insert) X
  - Other labeling in class (most recent 3) or class labeling..... N/A
  - Has DDMAC reviewed the labeling? ..... Yes ☒ No
  - Immediate container and carton labels X
  - Nomenclature review X

- Application Integrity Policy (AIP). This application ☐ is ☒ is not on the AIP.
  - Exception for review (Center Director's memo)..... N/A
  - OC Clearance for approval..... N/A

Continued ⇨

- Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review) — ☐ Materials requested in AP letter ☒NA

- Post-marketing Commitments — N/A
  - Agency request for Phase 4 Commitments — N/A
  - Copy of Applicant's commitments — N/A

- Was Press Office notified of action (for approval action only)? — ☐ Yes ☒ No
  - Copy of Press Release or Talk Paper — N/A

- Patent
  - Information [505(b)(1)] — X
  - Patent Certification [505(b)(2)] — X
  - Copy of notification to patent holder [21 CFR 314.50 (i)(4)] — N/A

- Exclusivity Summary — N/A

- Debarment Statement — X

- Financial Disclosure
  - No disclosable information — X
  - Disclosable information – indicate where review is located — X

- Correspondence/Memoranda/Faxes — X

- Minutes of Meetings — X
  - Date of EOP2 Meeting N/A
  - Date of pre NDA Meeting April 24, 2000
  - Date of pre-AP Safety Conference N/A

- Advisory Committee Meeting — N/A
  - Date of Meeting —
  - Questions considered by the committee —
  - Minutes or 48-hour alert or pertinent section of transcript —

- Federal Register Notices, DESI documents — N/A

CLINICAL INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo) — X

- Clinical review(s) and memoranda — X

Continued ⇨

- Safety Update review(s) X

- Pediatric Information
  ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred
  Pediatric Page..... N/A
  ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable

- Statistical review(s) and memoranda X

- Biopharmaceutical review(s) and memoranda..... X

- Abuse Liability review(s) ..... N/A
  Recommendation for scheduling .....

- Microbiology (efficacy) review(s) and memoranda ..... N/A

- DSI Audits X
  ☒Clinical studies ☐bioequivalence studies .....

CMC INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- CMC review(s) and memoranda X

- Statistics review(s) and memoranda regarding dissolution and/or stability ..... N/A

- DMF review(s) ..... N/A

- Environmental Assessment review/FONSI/Categorical exemption X

- Micro (validation of sterilization) review(s) and memoranda ..... N/A

- Facilities Inspection (include EES report)
  Date completed _____ ..... ☐ Acceptable ☒ Not Acceptable

- Methods Validation ..... ☐ Completed ☒ Not Completed

PRECLINICAL PHARM/TOX INFORMATION: **Indicate N/A (not applicable), X (completed), or add a comment.**

- Pharm/Tox review(s) and memoranda X

Continued ⇨

- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS
Ferring Pharmaceuticals Inc.
120 White Plains Road, Suite 400
Tarrytown, NY 10591

2. TELEPHONE NUMBER *(Include Area Code)*
(914) 333-8900

3. PRODUCT NAME
OVANEX™

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER
4033

6. LICENSE NUMBER / NDA NUMBER
N021289

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Ronald V. Mundi	Vice President Scientific & Regulatory	September 27, 2000

FORM FDA 3397 (5/98)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

INSTRUCTIONS FOR COMPLETING USER FEE COVER SHEET
FORM FDA 3397

Form FDA 3397 is to be completed for and submitted with each new drug or biologic product original application or supplemental application submitted to the Agency on or after April 27, 1998. Form 3397 should be placed in the first volume of the application with the application form. A copy of Form 3397 should be included with the fee payment.

ITEM NOS. **INSTRUCTIONS**

1-2. **Self-explanatory**

3. **PRODUCT NAME** - Include generic name and trade name, as applicable.

4. **CLINICAL DATA** - The definition of 'clinical data' for the assessment of user fees is found in Interim Guidance: Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees under the Prescription Drug User Fee Act of 1992.

5. **USER FEE I.D. NUMBER - PLEASE INCLUDE THIS NUMBER ON THE APPLICATION PAYMENT CHECK.** If the application is exempted from a fee, a User Fee I.D. Number is not required. To obtain the appropriate User Fee I.D. Number, read and complete the following:

FOR DRUG PRODUCTS - A unique identification number will be assigned to each submission. This individual identification number may be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

FOR BIOLOGIC PRODUCTS - The first 4 characters are the U.S. License Number, including leading zeros; the next 4 characters are the product code (2 letters followed by 2 numbers); and the last 7 characters are the date on the cover letter of the submission, in the format: DDMONYR. If the facility is unlicensed, or the product code is unknown, a number can be obtained by calling the Center for Biologics Evaluation and Research, at (301) 827-3503.

EXAMPLE: For U.S. License Number 4, product code XX01, with a document submission date of 8/3/93, the number would be: 0004XX0103AUG93.

6. **LICENSE NUMBER / NDA NUMBER**

FOR BIOLOGIC PRODUCTS - Indicate the U.S. License Number. If the facility is unlicensed, leave this section blank.

FOR DRUG PRODUCTS - Indicate the NDA number, including a leading zero. NDA numbers can be obtained by calling the Center for Drug Evaluation and Research, Central Document Room, at (301) 827-4210.

EXAMPLE: For NDA 99999, the number would be: NO99999.

7. **EXCLUSIONS:**

Section 505(b)(2) applications, as defined by the Federal Food, Drug, and Cosmetic (FD&C) Act, are excluded from application fees if: they are NOT for a new molecular entity which is an active ingredient (including any salt or ester of an active ingredient); or NOT a new indication for use.

The application is for an orphan product. Under section 736(a)(1)(E) of the FD&C Act, a human drug application is not subject to an application fee if the proposed product is for a rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation) AND the application does not include an indication that is not so designated. A supplement is not subject to an application fee if it proposes to include a new indication for a rare disease or condition, and the drug has been designated pursuant to section 526 for a rare disease or condition with regard to the indication proposed in the supplement.

The submission is a supplement for a new pediatric indication. Under section 736(a)(1)(F) of the FD&C Act, a supplement to a "human drug application" proposing to include a new indication for use in pediatric populations is not subject to a fee.

8. **WAIVER** - Complete this section only if a waiver of user fees, including the small business waiver, has been granted for this application. A copy of the official FDA notification that the waiver has been granted must be provided with the submission.

MODE = MEMORY TRANSMISSION START=JUL-27 16:04 END=JUL-27 16:06

FILE NO.=152

STN NO.	COMM.	ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
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-FDA/DRUDP -

********** -FDA/DRUDP - ***** - 301 827 4267- **********

TELEFAX

TO: Dr. Nardi

FAX: 914-631-5120

PHONE: 914333-8932

FROM: Dornette Spell-LeSane

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267
PHONE: (301) 827-4260

DATE: 7/27/01

PAGES: 5 (Inclusive)

TELEFAX

TO: Dr. Nardi

FAX: 914-631-5120

PHONE: 914333-8932

FROM: Dornette Spell-LeSane

Food and Drug Administration
Division of Reproductive and Urologic Drug Products
5600 Fishers Lane, HFD-580
Rockville, Maryland 20857-1706

FAX: (301) 827-4267
PHONE: (301) 827-4260

DATE: 7/27/01

PAGES: 5 (Inclusive)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 4/25/01	DUE DATE: 5/25/01	OPDRA CONSULT: 01-0092

TO:

Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH:

Dornette Spell-LeSane
Project Manager, Division of Reproductive and Urologic Drug Products
HFD-580

PRODUCT NAME:	**MANUFACTURER:** Ferring Pharmaceutical Inc.
Bravelle (Purified Urofollitropin for Injection, USP) 75 International Units (IU) **NDA #:** 21-289	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name "Bravelle" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:
OPDRA has no objection to the use of the proprietary name, "Bravelle". See the checked box below.

☐ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☒ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approval of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3242
Fax: 301-480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 23, 2001

NDA NUMBER: 21-289

NAME OF DRUG: Bravelle (Purified Urofollitropin for Injection), 75 International Units (IU)

NDA HOLDER: 21-289

I. INTRODUCTION:

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580) for assessment of the tradename "Bravelle". "Bravelle" is the second name the sponsor submitted to the Agency since the sponsor's prior submitted tradename, "Ovanex", was unacceptable to OPDRA (see OPDRA consult #00-0326).

PRODUCT INFORMATION

"Bravelle" is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. In conjunction with human chorionic ganadotropin (hCG), "Bravelle" is indicated for multiple follicular development (controlled ovarian stimulation) and ovulation induction in patients who have previously received pituitary suppression. In order to stimulate the development of ovarian follicles, the dose of "Bravelle" must be individualized for each patient. The recommended initial dose for infertile patients with oligo-anovulation is 150 IU daily for the first 5 days of treatment. The recommended dose for patients who are undergoing assisted reproductive technologies is 225 IU. 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 "Bravelle" should not exceed 450 IU, and, in most cases, dosing beyond 12 days is not recommended. "Bravelle" will be available in packages containing 5 and 100 vials each of purified urofollitropin for injection in addition to sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "Bravelle" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent

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[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood. Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Bravelle". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with "Bravelle". These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1

Product Name	**Dosage form(s), Generic name**	**Usual adult dose***	**Other****
Bravelle	Purified Urofollitropin for Injection (Fertility Hormone – Rx) Injection: 75 IU	*Infertile patients with oligo-anovulation:* 150 IU daily for the first 5 days of treatment. *Assisted reproductive technologies:* 225 IU daily.	
Vivelle	Estradiol (Hormone – Rx) Transdermal: 0.025 mg/24 hr, 0.0375 mg /24 hr, 0.05 mg/24 hr, 0.075 mg/24 hr, 0.1 mg/24 hr.	Apply patch (0.025 mg – 0.05 mg/24 hr) to skin twice a week.	S/A, L/A per OPDRA
Provol	*Pygeum africanum* (Dietary Supplement – OTC) Capsule: 50 mg	One capsule twice a day.	S/A per OPDRA
Brevital Sodium	Methohexital Sodium (Barbiturate, General Anesthetic – Rx) Powder for Injection: 500 mg, 2.5 g, 5 g	*Induction:* 1-1.5 mg/kg (1% solution at 1 mL/5 seconds).	S/A, L/A per OPDRA
Brevoxyl	Benzoyl Peroxide (Anti-Infective – Rx) Gel and Cleansing Lotion: 4% and 8%	Apply once or twice a day.	S/A per OPDRA
		*Frequently used, not all-inclusive	**S/A(Sound-alike), L/A (Look-alike

B. PRESCRIPTION ANALYSIS STUDIES

[5] WWW location http:// www.uspto.gov/tmdb/index.html.

1. Methodology:

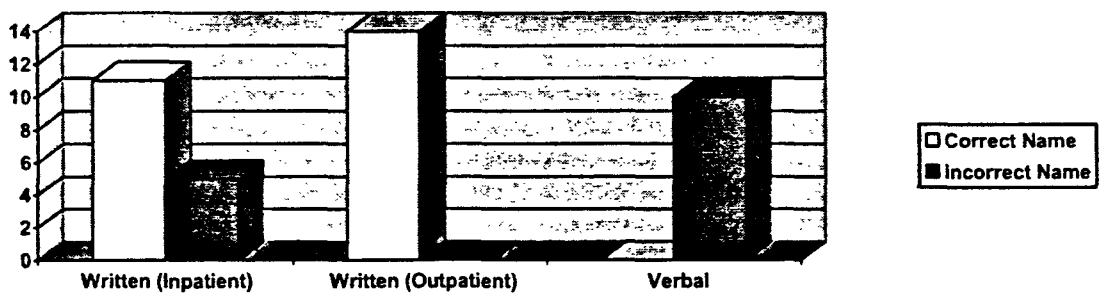
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Bravelle" and with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 85 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient prescription and one outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for "Bravelle" (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
"Bravelle"	
Inpatient: Bravelle 150 IU SQ daily x 5 days #10	*Outpatient:* Bravelle, 150 IU sub-Q, once a day for 5 days, #10.
Outpatient: Bravelle 150 IU SQ QD x 5 days #10	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted "Bravelle"	Incorrectly Interpreted
Written: Inpatient	28	16 (57%)	11 (69%)	5 (31%)
Outpatient	27	14 (52%)	14 (100%)	0 (0%)
Verbal: Outpatient	30	10 (33%)	0 (0%)	10 (100%)
Total	85	40 (47%)	25 (62%)	15 (38%)



Among the written inpatient prescriptions, 5 (31%) out of 16 respondents interpreted "Bravelle" incorrectly. Interpretations included *Bramile, Bavelle, Branlle,* and *Branke.*

Among the written outpatient prescriptions, all of the 14 respondents (100%) interpreted "Bravelle" correctly. However, one respondent commented that the proprietary name "Bravelle" sounds like an oral contraceptive medication.

Among the verbal outpatient prescriptions, all of the 10 respondents (100%) interpreted "Bravelle" incorrectly. Interpretations included *Bervel, Brevel, Brevelle, Burvel, Broval, Brovel,* and *Brovell.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Bravelle", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Such names that sound and look similar to "Bravelle" include *Brevoxyl, Brevital, Provol,* and *Vivelle.*

Brevoxyl is a topical anti-infective indicated for mild to moderate acne vulgaris. *Brevoxyl* and "Bravelle" sound similar to each other since "brev" and "brav" sound alike and both proprietary names end with an "l" sound. However, *Brevoxyl* contains three syllables while "Bravelle" only has two, and *Brevoxyl* can be distinguished from "Bravelle" by the sound of its "x". The dosage forms between "Bravelle" and *Brevoxyl* are different (injection vs. gel and lotion) as well as the strengths (75 IU vs. 4% and 8%) and the directions of use (SQ or IM daily vs. Apply to skin once or twice a day). These differences would lower the potential risk of a medication error between these two products.

Brevital Sodium is a barbiturate, which is used as a general anesthetic. *Brevital* may slightly resemble "Bravelle" in writing depending on how the proprietary name is scripted. *Brevital* and "Bravelle" also sound similar since the sounds "brev" and "brav" sound alike and both appear at the beginning of the two proprietary names. In the verbal portion of the OPDRA study, some respondents interpreted the "brav" in "Bravelle" as "brev" (*Brevelle, Brevel*). Also, the "elle" in "Bravelle" can be interpreted as "al", which can be seen in the verbal portion of the OPDRA study (*Broval*). However, *Brevital* may be distinguished from "Bravelle" by the sound of the "t" in *Brevital*. Both drug products are available as powder for injection; however, *Brevital* is available in three strengths (500 mg, 2.5 g, and 5 g) while "Bravelle" is only available in one strength with a different type of measuring units (75 International Units) though 75 IU may be interpreted as *Brevital* 75 mg IV. The settings where the two drug products are dispensed may be different. "Bravelle" may mainly be dispensed by a community pharmacy since the patient can self-administer the drug. *Brevital* is usually dispensed by a hospital pharmacy since general anesthesia is generally used in a hospital setting. Due to the slight differences in the two proprietary names when scripted and pronounced verbally and the different settings where the products are available, the potential risk of medication errors occurring is decreased.

Provol is considered a nutraceutical dietary supplement that claims to help maintain a healthy prostate. *Provol* does sound similar to "Bravelle". Some respondents in verbal portion of the OPDRA study interpreted "Bravelle" as *Broval, Brovel, and Brovell,* which are very similar to *Provol*. However, there are many differences between the two products that may decrease the potential risk of a medication error from occurring. *Provol* is available in a 50-mg capsule while "Bravelle" is available as a 75 International Units injectable. The dosage forms, route of administration, and the strengths are different. Also, *Provol* is recommended to be taken twice a day while "Bravelle" is given once a day. "Bravelle" is available by prescription only while *Provol* is available over-the-counter.

Vivelle is a transdermal estrogen patch indicated for moderate-to-severe vasomotor symptoms associated with menopause, female hypogonadism, female castration, primary ovarian failure, atrophic conditions caused by deficient endogenous estrogen production, atrophic urethritis, prevention of osteoporosis, abnormal uterine bleeding due to hormonal imbalance in the absence

of organic pathology and only when associated with a hypoplastic or atrophic endometrium. *Vivelle* and "Bravelle" look and sound similar mainly due to the "velle" ending on both proprietary names. Both proprietary names also contain two syllables. However, if "Bravelle" was mistaken for *Vivelle*, a strength or rate of release would have to be indicated on the prescription since *Vivelle* is available in multiple strengths or rates of release. "Bravelle" and *Vivelle's* dosage forms are different (injection vs. transdermal patch) as well as the route of administration (parenteral vs. topical) and directions of use (once a day vs. twice a week). Due to these differences, the potential risk of medication errors occurring between these two products is low.

OPDRA has no objections to the use of the proprietary name "Bravelle".

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

General Comment

The proprietary name is stated as "Bravelle 75 IU". Please revise it to state "Bravelle 75 International Units" since the IU can be misinterpreted as IV (intravenous).

A. CONTAINER LABEL

1. See General Comment above.

2. The print on the NDC number is too small to read. Please use a larger font size for the NDC number.

B. CARTON LABELING (5 and 100 vials)

1. See General Comment above.

2. As per OPDRA consult #00-0326, the reconstitution instructions "Reconstitute with *1 to 2 mL* of 0.9% Sodium Chloride Injection, USP" is too vague since the exact amount of sodium chloride is not provided. The instructions should state the exact amount of Sodium Chloride that needs to be added to the drug for subcutaneous and intramuscular administration:

   For subcutaneous injection, reconstitute with ... mL of 0.9% Sodium Chloride Injection, USP.

   For intramuscular injection, reconstitute with ... mL of 0.9% Sodium Chloride Injection, USP.

C. PACKAGE INSERT

1. See General Comment above.

2. As per OPDRA consult #00-0326, the Administration section under DOSAGE AND ADMINISTRATION states to dissolve one or more vials of Bravelle in *one-half to one mL* of

sterile saline for injection (concentration should not exceed 225 IU/0.5 mL). This statement is inconsistent to the reconstitution instructions on the carton labeling (see CARTON LABELING comment #2). The reconstitution instructions should be clear and consistent.

3. In the same statement above (PACKAGE INSERT comment #2), it would be difficult to get a total concentration of 225 IU/0.5 mL. Since one vial contains 75 IU, does the sponsor recommend in adding 0.5 mL of sterile saline for injection to one vial, withdraw the total contents of that vial and add it to another vial containing 75 IU of Bravelle, and then add the total of those contents to another vial of Bravelle? Is it possible to dissolve 225 IU of Bravelle in 0.5 mL of sterile saline?

4. The statement "Administer subcutaneously or intramuscularly immediately after reconstitution" should be stated in the beginning of the DOSAGE AND ADMINISTRATION section.

5. As per OPDRA consult #00-0326, the first sentence under the Assisted Reproductive Technologies section (DOSAGE AND ADMINISTRATION) should be revised to include a dose frequency:

   ... is 225 International Units daily. Based ...

IV. RECOMMENDATIONS:

A. OPDRA has no objections to the use of the proprietary name "Bravelle".

B. OPDRA recommends the above labeling revisions to encourage the safest possible use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Jennifer Fan, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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

/s/

Jennifer Fan
5/25/01 11:47:52 AM
PHARMACIST

Jerry Phillips
5/25/01 11:55:14 AM
DIRECTOR

Martin Himmel
5/30/01 01:00:06 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO: **Office of Postmarketing Drug Assessment (HFD 400)** **Attention: Sammie Beam** Room # 15B23.			FROM: HFD-580 (Division of Reproductive and Urologic Drug Products) Dornette Spell-LeSane, Regulatory Project Manager	
DATE: **April 25, 2001**	IND NO.:	NDA NO.: 21-289	TYPE OF DOCUMENT: Tradename review	DATE OF DOCUMENT: **April 20, 2001**
NAME OF DRUG: **Ovanex** **Bravelle**	PRIORITY CONSIDERATION: **standard**		CLASSIFICATION OF DRUG: **urofollitropin**	DESIRED COMPLETION DATE: **June 25,2001**

NAME OF FIRM: **Ferring Pharmaceuticals**

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY

☐ PRE--NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT

☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
X OTHER *(SPECIFY BELOW)*:
NDA Tradename Review

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

☐ DISSOLUTION
☐ BIOAVAILABILTY STUDIES
☐ PHASE IV STUDIES

☐ DEFICIENCY LETTER RESPONSE
☐ PROTOCOL-BIOPHARMACEUTICS
☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ SUMMARY OF ADVERSE EXPERIENCE
☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review revised tradename. In the original consult # 00-0326, OPDRA did not recommend the use the proprietary name "Ovanex". The sponsor has submitted a new name for review. **The 10-month goal date is July 29, 2001.**

cc: Original NDA 21-289
HFD-580/Div. Files
HFD-580/Bennett/Spell-LeSane/Sla ughters/Olmstead/Rumblet/
HFD 510/Haber

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): ☐ MAIL HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

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

/s/

Dornette Spell-LeSane
4/25/01 05:21:19 PM

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: December 20, 2000	**DUE DATE:** June 1, 2001	**OPDRA CONSULT #:** 00-0326

TO: Susan Allen, MD
Director, Division of Reproductive and Urologic Drug Products
HFD-580

THROUGH: Freshnie DeGuia, Project Manager
HFD-580

PRODUCT NAME:	**DISTRIBUTOR:** Ferring Pharmaceutical Inc.
Ovanex (Purified Urofollitropin for injection, USP) 75 IU **NDA #: 21-289**	

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Reproductive and Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name "Ovanex" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Ovanex".

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
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Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **February 28, 2001**

NDA NUMBER: **21-289**

NAME OF DRUG: **Ovanex**
(Purified Urofollitropin For Injection, USP)
75 IU

NDA HOLDER: **Ferring Pharmaceuticals, Inc.**

I. INTRODUCTION

This consult was written in response to a request from the Division of Reproductive and Urologic Drug Products (HFD-580), for assessment of the tradename "Ovanex", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION
Ovanex is a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. Ovanex in conjunction with human chorionic Ganadotropin (hCG) is indicated for multiple follicular development (controlled ovarian stimulation) and ovulation induction in patients who have previously received pituitary suppression. The dose of Ovanex to stimulate development of ovarian follicles must be individualize for each patient. However, the recommended initial dose of Ovanex for infertile patients with oligo-anovulation is 150 IU daily for the first 5 days of treatment. The recommended dose for patients who are undergoing assisted reproductive technologies is 225 IU. 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 Ovanex should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended. Ovanex will be available in packages containing 5 and 100 vials each of purified urofollitropin for injection in addition to sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale

sound-alike or look-alike to "Ovanex" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Ovanex". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Five product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Ovanex. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns with the name in regard to promotional claims.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Ovanex	Purified Urofollitropin for injection, USP (Rx)	*Infertile patients with oligo-anovulation*: 150 IU daily for the first 5 days of treatment. *Assisted reproductive technologies*: 225 IU daily.	
Avonex	Interferon Beta-1A powder for injection 33 mcg (Rx)	30 mcg once a week	S/A, L/A per OPDRA
Avelox	Moxifloxacin 400 mg tablets (Rx)	400 mg once daily for 5 to 10 days (duration of therapy depends on severity of infection)	S/A, L/A per OPDRA

(Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

[v] WWW location http://www.uspto.gov/tmdb/index.html.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Ovanex	Purified Urofollitropin for injection, USP (Rx)	*Infertile patients with oligo-anovulation*: 150 IU daily for the first 5 days of treatment. *Assisted reproductive technologies*: 225 IU daily.	
Vanex	***Expectorant***: Psuedoephidrine 30 mg, guiafenisin 100 mg, 2.5 mg hydrocodone (CIII) ***Forte***: PPA 50 mg, phenylephrine 10 mg, 4 mg chlorpheneramine, 25 pyrilamine (Rx) ***Forte-R***: PPA 75 mg, chlorpheneramine 12 mg (Rx) ***HD Liquid***: phenylephrine 5 mg, chlorpheneramine 2 mg, 1.67 mg hydrocodone (CIII)	Expectorant: 10 mL every 4-6 hours Forte: 1 capsule 2-3 times daily Forte-R: 1 capsule every 12 hours HD Liquid: 10 mL 3 times daily	S/A, L/A per OPDRA
Uvadex	Methoxsalen solution 20 mcg/mL (Rx)	10ml extracorporeally administered for 2 consecutive days every 4 weeks for a minimum of 7 treatment cycles (6 months)	S/A, L/A per OPDRA
Ornex	Pseudoephedrine 30 mg/ acetaminophen 500 mg (Otc)	2 tablets every 4 hours (up to 8/day)	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

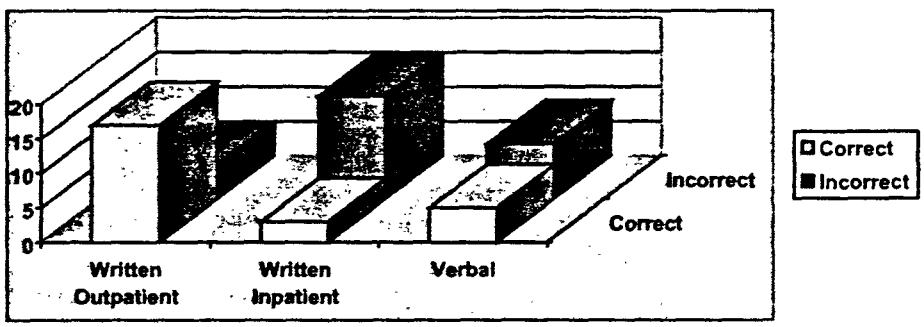
A study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of Ovanex with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. OPDRA staff members wrote an inpatient and an outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for Ovanex (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Ovanex 150 IU Sig: 150 IU SC qd x 12d Disp #1	Ovanex 150 IU 150 IU subcutaneously once daily for 12 days Dispense #1
Inpatient: Ovanex 150 IU SC	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Ovanex" response	Other response
Written: Outpatient	28	22 (79%)	17 (77%)	5 (23%)
Inpatient	28	18 (64%)	3 (17%)	15 (83%)
Verbal: Outpatient	30	13 (43%)	5 (38%)	8 (72%)
Total:	86	53 (62%)	25 (47%)	28 (53%)



Among the participants in the written prescription studies, 20 out of 40 respondents (50%) interpreted the name incorrectly. The interpretations were misspelled/phonetic variations of "Ovanex", such as *Oramax, Ovamax, Ovanox, Ovanor,* and *Ovunex*. **Fourteen study participants responded with *Oranex* as as interpretation.**

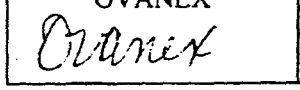
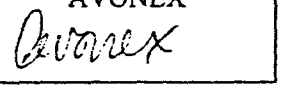
Among the verbal prescription study participants, 8 out of 13 (62%) of the participants interpreted the name incorrectly. Some of the incorrect name interpretations were phonetic variations of "Ovanex" such as *Ovonex, Ovenex,* and *Ovalix.*

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Ovanex", the primary concerns raised were related to a couple sound-alike, look-alike name that already exists in the U.S. marketplace. Four products, Avonex, Avelox, Ornex, and Vanex were believed to be the most problematic in terms of potential medication errors.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Ovanex could be confused with Avonex, Avelox, or Vanex. However 14 study participants (64%) from the inpatient prescription study provided Oranex as an interpretation, which is very similar to the approved drug product Ornex. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The majority of the written prescriptions were phonetic variations of the drug name Ovanex.

Avonex is the proprietary name for interferon beta-1a and is produced by recombinant DNA technology. Avonex is indicated for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. The recommended dosage of Avonex for the treatment of relapsing forms of multiple sclerosis is 30 mcg injected intramuscularly once a week. In regard to differences in comparing Ovanex and Avonex, the drug products vary in strength and dosing schedule. However, despite these differences, many similarities exist between the two products. For example, both Ovanex and Avonex are supplied as a lyophilized powder and need to be reconstituted, both products share an overlapping route of administration (IM), and both products sound and look very similar to one another (see writing sample below). Furthermore, because these two drug products are available in one strength and possess atypical dosing schedules, prescribers may omit the strength and write "use as directed" for the directions on the prescription. Moreover, despite the fact that these drug products are restricted to special populations, postmarketing experience has demonstrated errors occurring between two drug products with varying indications for use. For example, Depo-Provera (injectable contraceptive) has been inadvertantly confused for Depo-Medrol and Lupron-Depot for Rhogam. Severe and life-threatening consequences may arise from the confusion of Ovanex and Avonex. Avonex has been known to exacerbate seizure disorders, depression with suicidal tendencies, and cardiac diseases, such as angina, congestive heart failure, or arrhythmia. Ovanex has been identified to cause complicated ovarian enlargement in women and pulmonary and vascular complications.

OVANEX	AVONEX
	

Other drugs names that have a high potential for confusion with Ovanex include Avelox, Ornex, Uvadex and Vanex. Despite the fact that Ovanex and the above mentioned drug names differ in route of administration (injection vs. oral, inhalation), a possibility of confusion does exist because of a look alike and sound alike potential. Postmarketing experience has demonstrated actual errors occurring between injectable and oral drug products with similar names. For example, Cerebyx injection and Celebrex capsules have been confused for one another even though the drugs differ

in strength, dosage form, dosing regimen, and route of administration. Furthermore, fourteen respondents provided Oranex as an interpretation to the written inpatient prescription studies conducted by OPDRA. Oranex is strikingly similar to the drug name Ornex. Therefore, given the similarities in drug name between Ovanex and Avelox, Ornex, Uvadex, and Vanex, a potential for confusion does exist.

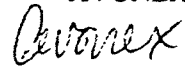
III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft container label and draft package insert for Ovanex, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvements, in the interest of minimizing potential user error and refer you to section IV. In particular, the abbreviation IU is dangerous and has been linked to numerous errors where IU was interpreted as IV. We are recommending that the abbreviation IU not be used but instead spelled out as "International Units" when possible if space permits.

IV. COMMENTS TO BE PROVIDED TO THE SPONSOR

OPDRA does not recommend the use of the drug name Ovanex.

The potential for confusion between Ovanex and Avonex is significant. For example, both Ovanex and Avonex are supplied as lyophilized powder and need to be reconstituted, both products share an overlapping route of administration (IM), and both products sound and look very similar to one another (see writing sample below). Furthermore, because these two drug products are available in one strength and possess atypical dosing schedules, prescribers may omit the strength and write "use as directed" for the directions on the prescription. Moreover, despite the fact that these drug products are restricted to special populations, postmarketing experience has demonstrated errors occurring between two drug products with varying indications for use. For example, Depo-Provera (injectable contraceptive) has been inadvertantly confused for Depo-Medrol and Lupron-Depot for Rhogam.

OVANEX	AVONEX
	

Other drugs names that have a high potential for confusion with Ovanex include Avelox, Ornex, Uvadex and Vanex. Despite the fact that Ovanex and the above mentioned drug names differ in route of administration (injection vs. oral, inhalation), a possibility of confusion does exist because of a look alike and sound alike potential. Postmarketing experience has demonstrated actual errors occurring between injectable and oral drug products with similar names. For example, Cerebyx injection and Celebrex capsules have been confused for one another even though the drugs differ in strength, dosage form, dosing regimen, and route of administration. Furthermore, fourteen respondents provided Oranex as an interpretation to the written inpatient prescription study conducted by OPDRA. Oranex is strikingly similar to the drug name Ornex. Therefore, given the similarities in drug name between Ovanex and Avelox, Ornex, Uvadex, and Vanex, a potential for confusion does exist.

LABELING, PACKAGING AND SAFETY RELATED ISSUES

1. CONTAINER LABEL

   a. We recommend placing the established name in conjunction with the proprietary name so it appears directly beneath the proprietary name.

   b. Per 21 CFR 201.1(g)(2) the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name.

   c. Relocate the Expiration Date so it does not appear in conjunction with the concentration.

2. CARTON LABELING

   a. See comments under container label.

   b. A statement on the bottom panel reads to "Reconstitute with *1 to 2 mL* of 0.9% Sodium Chloride Injection, USP." These instructions are vague because "1 to 2 mL" does not instruct users to reconstitute with an exact amount. We recommend including an exact volume for reconstitution. The package insert states to dissolve the contents in *one-half to one mL* sterile saline for injection. This quantity is not consistent with the quantity on the carton labeling. Revise all statements so that a consistent and exact amount is cited for reconstitution.

   c. We prefer that you relocate the NDC number so it appears on the upper right or left hand corner of the label.

3. PACKAGE INSERT (DOSAGE AND ADMINISTRATION; Assisted Reproductive Technologies)

   Revise the first sentence to include a dose frequency, as follows:

   ...is 225 International Units daily. Based...

V. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name "Ovanex".

B. ODRA has recommended labeling interventions that might minimize user error.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

/s/

Alina Mahmud
3/7/01 02:59:39 PM
PHARMACIST

Jerry Phillips
3/7/01 03:23:03 PM
DIRECTOR

Martin Himmel
3/13/01 03:58:04 PM
MEDICAL OFFICER

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

REQUEST FOR CONSULTATION

) *(Division/Office)*: OPDRA; HFD-400
Attention: Sammie Beam, Room 15B03

FROM: HFD-580 (Division of Reproductive and Urologic Drug Products) Freshnie DeGuia, Regulatory Project Manager

DATE:	IND NO.:	NDA NO.:	TYPE OF DOCUMENT:	DATE OF DOCUMENT:
December 18, 2000		21-289	New NDA	September 28, 2000

NAME OF DRUG:	PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE:
OVANEX (urofollitropin for injection)	S	gonadotropin	**June 1, 2001**

NAME OF FIRM: Ferring Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: This is a request for a tradename review for this new NDA. The User Fee Goal Date is July 29, 2001.

cc: Original NDA 21-289
HFD-580/Div. Files
HFD-580/EDeGuia/TRumble/MRhee
HFD-510/DWu/MHaber

SIGNATURE OF REQUESTER:	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER:	SIGNATURE OF DELIVERER:

/s/

Eufrecina deGuia
12/20/00 09:14:09 AM

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 14

❖❖❖

Draft Labeling
(not releasable

14.0 A PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG (21 U.S.C. 355 (B) (2) OR (J) (2) (A))

In the opinion and to the best knowledge of Ferring Pharmaceuticals Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

The purified FSH drug substance is the subject of a patent application Number 60/129540 to which Ferring Pharmaceuticals Inc. has the rights in the United States.

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

APPEARS THIS WAY
ON ORIGINAL

13.0 PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG (21 U.S.C. 355 (B) OR (C))

In the opinion and to the best knowledge of Ferring Pharmaceuticals Inc., there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

The purified FSH drug substance is the subject of a patent application Number 60/129540 to which Ferring Pharmaceuticals Inc. has the rights in the United States.

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

APPEARS THIS WAY
ON ORIGINAL

NDA 21-289

Exclusivity Summary not completed at this time due to not approvable action.

16.0 DEBARMENT STATEMENT

Debarment Certification

Ferring Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

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

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

2 pages

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

/s/

Jeanine Best
5/3/01 02:33:54 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See List Attached	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Ronald V. Nardi, Ph.D	Vice Pres., Regulatory & Scientific Affairs
FIRM/ORGANIZATION	
Ferring Pharmaceuticals, Inc.	120 White Plains Rd., Suite 400 Tarrytown, NY 10591
SIGNATURE	**DATE**
Ronald V. Nardi	10/9/00

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

1 page

19.0 FINANCIAL DISCLOSURE

Ferring Pharmaceuticals Inc. hereby certifies that Financial Disclosures for all Clinical Investigators have been received and are filed as appropriate.

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

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

PHARMACEUTICALS

July 19, 2001

NDA ORIG AMENDMENT

Susan Allen, 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

WBC

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 20 2001
HFD-580

RE: NDA # 21-289 Bravelle™ (urofollitropin for injection), Amendment
FSH (urofollitropin)

Dear Dr. Allen

Enclosed please find an amendment to the above referenced NDA. This amendment contains additional responses to items in the request for information letter received on July 9, 2001 from Dr. Rhee. With this amendment we have completed the responses to all data questions except items:

- 4f (English translation of the batch record for drug substance),
- 5b (batch size, storage and stability data for the reference standard) and
- 5c (certificates of analysis and supporting data for the reference standard).

A separate labeling amendment will be submitted to address items 13 and 14 in Dr. Rhee's letter.

We are continuing to use the numbering scheme from Dr. Rhee's letter to identify the question and our response. In this submission the tab labeled to correspond to the item in Dr. Rhee's list contains each question along with our response. For multipart questions, sub-tabs separate the support data. A table of contents is attached to this cover letter.

For those items to which we have responded, we believe the responses satisfy the specific request for information. If you need additional information, please contact me at 914-333-8932 or by fax at 914-631-5120.

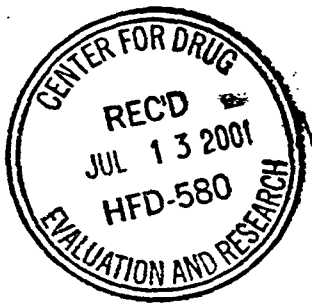
Sincerely

Ronald V. Nardi

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

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

NDA ORIG AMENDMENT

July 11, 2001

DUPLICATE

Susan Allen, 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

N-B C

RE: NDA # 21-289 Bravelle™ (urofollitropin for injection), Amendment
_____, FSH (urofollitropin)

Dear Dr. Allen

Enclosed please find an amendment to the above referenced NDA. This amendment contains responses to some of the items in the request for information letter received on July 9, 2001 from Dr. Rhee. As you know the list is lengthy and as you might expect some of the information is readily available. This particular amendment will focus on the requests for which the responses are relatively short and easy to address.

It is our belief that it will require 2 or 3 submissions to respond to all requests. Consequently, we will use the numbering scheme from Dr. Rhee's letter to identify the question and our response.

1. **Please provide an English translation of the amendment dated February 15, 2001 (submitted in Spanish).**

   Translations of the previously submitted SOPs (Spanish versions) are attached (see tab labeled 1)

2. **With regard to the Characterization of the Drug Substance (Urofollitropin, purified), please provide the following:**

   a. **For the isolated α and β subunits, comparison of the amino acid composition obtained from your experimental analysis to the theoretical composition predicted from the sequences.**

      The α-subunit and β-subunit sequences determined for Bravelle™ correspond to the sequences reported in literature and the information was included in amendment 006 dated April 5, 2001 as described below.

      The α-subunit sequence determined for Bravelle™ is located in NDA amendment 006 (Volume 4K), April 5, 2001, page 48. The sequence

Ferring Pharmaceuticals Inc., 120 White Plains Road, Suite 400, Tarrytown, New York 10591, U.S.A.
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US

FERRING
PHARMACEUTICALS

July 11, 2001

DUPLICATE

Susan Allen, MD
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

NDA ORIG AMENDMENT

N-15 M

RE: NDA #21-289, Amendment S019

Dear Dr. Allen:

Ferring is submitting this amendment to NDA #21-289 for Bravelle®. The amendment consists of brief clinical summaries for the twelve cases of Ovarian Hyperstimulation Syndrome rated non-serious in this clinical program in studies FPI FSH 99-03, 99-04 and 99-05. These include two cases in the Follistim® group. The individual study reports and the previous amendment S017 contain clinical summaries of the 7 cases of OHSS rated serious (required hospitalization).

Ferring has also provided, in previous submissions, the case report forms for all 19 cases of OHSS (including those related to Follistim®) observed in this program.

We hope this provides the information you have requested. Please contact us with any further questions.

Sincerely,

Ronald V. Nardi

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

Bravelle™ and should replace the tables from March 1, 2001 in Volume 3A1, Section IX and Volume 9A1, Section III. We regret any inconvenience which these discrepancies caused in your review of the Bravelle™ NDA.

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

Sincerely,

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

APPEARS THIS WAY
ON ORIGINAL

US

FERRING
PHARMACEUTICALS

July 5, 2001

Susan Allen, 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

RE: NDA #21-289, Amendment #018 Draft Labeling

Dear Dr. Allen:

Ferring is submitting the enclosed Amendment #018 to NDA 21-289. It consists of a revised package insert changing the generic name of the drug product from Purified h Follitropin for Injection to urofollitropin for injection, purified and revising the urofollitropin to Bravelle™ in several places throughout the text of the Package Insert as per FDA's directions.

Please contact us if you have any additional questions.

Sincerely,

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

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

June 29, 2001

DUPLICATE

Susan Allen, MD
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

BM
NDA ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 0 2 2001
HFD-580

RE: NDA #21-289, Amendment S018

Dear Dr. Allen:

Ferring is submitting this amendment to NDA #21-289. It consists of the following:

- Photocopies of 11 CRFs of patients with OHSS rated as non-serious in the Bravelle program. The breakdown by study and treatment group is:

Study Number	FSH SC	FSH IM	Follistim
99-03	2	2	2
99-04	3	2	0
99-05	1	-	-

- Photocopies of brief narratives excerpted from the 3 study reports of the 7 patients with OHSS rated serious. These consist of 4 from 99-03 (2 FSH SC, 2 Follistim), 1 from 99-04 (FSH IM) and 2 from 99-05 (FSH SC). We prepare these clinical summaries and incorporate them in our study reports because they describe hospitalizations not captured in the CRFs.

The Case Report Forms for the 7 cases of serious OHSS have already been submitted to the NDA and can be located in Volumes 12 A and B, of the original submission dated September 28, 2000 for 99-03 and 99-04 and in Volume 12C, of the submission dated March 1, 2001 (S 004) for study 99-05.

We have included the CRFs for the 2 non-serious OHSS cases in the Follistim group from 99-03 in this submission for your reference.

Please contact us with any questions, (914) 333-8932.

Sincerely,

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

FDA Form 356H
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Case Report Forms

FERRING
PHARMACEUTICALS

June 27, 2001

ORIGINAL

Susan Allen, 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

ORIG AMENDMENT

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Re: NDA 21-289, Bravelle™ (urofollitropin for injection, purified)
Amendment No. 016

Dear Dr. Allen:

Enclosed please find an amendment to the above referenced NDA. This amendment responds to issues discussed in several teleconferences with Dr. Duu Gong Wu regarding the review of the chemistry, manufacturing and controls sections of this NDA.

Dr. Wu requested that we change the established name to "urofollitropin for injection, purified" and we agreed. Dr. Wu further requested that we perform isoelectric focusing to compare the isoform composition of Bravelle and Fertinex®. These experiments will be performed as soon as possible and the results will be submitted to the NDA.

Dr. Wu requested and we agreed to the following changes to the specifications:

- Add a drug substance release specification for ——— based upon ———
- Change the oxidized forms specifications for drug substance, drug product and stability to percent of total α-subunits instead of percent of total urinary follitropin.
- Add a specification for aggregates to the drug product release specification and to the drug product stability protocol; this specification is already present for drug substance.
- Remove all specifications for ———
  - ———
- Change the specifications for reference standards in accordance with the above.

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

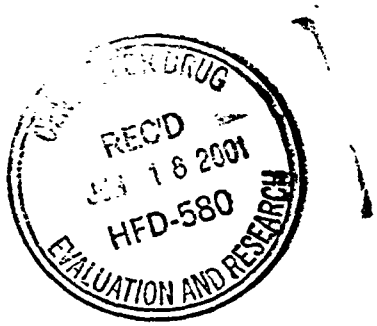
The following sections of this amendment include the revised specifications and the data to support them.

We appreciate your prompt review of this material. If you have any questions please do not hesitate to call me at (914) 333-8932.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL



FERRING
PHARMACEUTICALS

June 14, 2001

DUPLICATE

Susan Allen, 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

SU
NDA ORIG AMENDMENT

RE: NDA #21-289, Amendment #015

Dear Dr. Allen:

Ferring is submitting the enclosed updated Safety Summary as Amendment #015 to the Bravelle™ NDA.

The amendment consists of a single table summarizing all patients with any adverse events in the three patient studies of Bravelle, FPI FSH 99-03 (111 patients), FPI FSH 99-04 (177 patients) and FPI FSH 99-05 (30 patients). This table is identical to Table 7 in the most recent package insert submitted as Draft Labeling Amendment #S014 on June 8, 2001.

There are a few discrepancies with an earlier summary table of patients with AEs submitted on March 1, 2001 as Amendment S004 which appeared in two places: Volume 3A1, Section IX – Safety Summary and Volume 9A1, Section III – Pooled Safety. The differences consist of numerical changes in the number of patients with vaginal hemorrhage (8 instead of 11 in Bravelle™ SC and 6 instead of 8 in Bravelle™ IM); OHSS (10 instead of 9 in Bravelle ™ SC); Pain (4 instead of 6 in Bravelle™ SC); Ovarian Disorder (2 instead of 5 in Bravelle™ SC); Enlarged Abdomen (3 instead of 1 in Bravelle™ SC, 1 instead of 0 in Bravelle™ IM and 2 instead of 0 in Follistim SC) and Bone Pain (2 instead of 0 in Follistime SC).

There are two reasons for these discrepancies. Firstly, in reviewing the statistical tabulations, we noted certain AEs such as OHSS were consolidated into the less specific category of Ovarian Disorder. We concluded it was more accurate and informative to separate these into itemized categories. Secondly, a few arithmetic errors were made in tallying the numbers of patients with certain AEs across the three patient studies. The differences were not caused by any new clinical data.

The revised "Patients with Adverse Events" table, identical to Table 7 in the most recent package insert, represents all adverse events observed in the patient studies of

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

Bravelle™ and should replace the tables from March 1, 2001 in Volume 3A1, Section IX and Volume 9A1, Section III. We regret any inconvenience which these discrepancies caused in your review of the Bravelle™ NDA.

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

Sincerely,

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

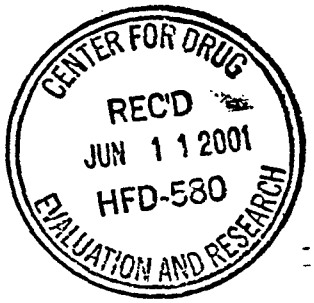
DUPLICATE

N-289

FERRING
PHARMACEUTICALS

June 8, 2001

Susan Allen, M.D.
irector
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



RE: NDA #21-289, Amendment #014

Dear Dr. Allen:

Attached please find a labeling amendment to the above referenced NDA. This amendment responds to the communication received from the agency on June 5, 2001. Please note that most of the recommendations from the FDA have been incorporated.. The version we are now submitting does contain some additional changes, which we believe are appropriate and strengthen the informational function of the label. These changes include the following:

- Efficacy and safety tables are presented representing the clinical studies in their entirety as randomized, 3 treatment group trials with a commercial recombinant FSH drug product as the active control. This more fully presents the studies' results, establishes better clinical context for medical end users and follows the conventions which FDA established in the Follistim and Gonal-F package inserts.
- Efficacy results for the uncontrolled ART study in donor egg patients are presented in a small table. This study (FPI FSH 99-05) was a formal, IND study with a complete study report submitted to the NDA in March 2001. It evaluated a different patient population than the FPI FSH 99-04 IVF study, which is younger, healthier and more physiologically responsive to gonadotropins. These egg donors required less Bravelle™ than the other IVF patients and had a slightly higher incidence of OHSS. The new version of the package label, which we are submitting, provides this important clinical information to assist reproductive endocrinologists in the safe and effective use of Bravelle.
- The chemical name of Bravelle™ has been changed from purified urofollitropin to ——— ———. Our discussions with USAN and the CAS registry leads us to conclude that ——— urofollitropin will not be acceptable as the generic name for Bravelle™. We are pursuing ——— ——— as the generic name.

We believe the revised package label contained in this submission is the most comprehensive, useful, informative and balanced presentation of the clinical data generated in our Bravelle program and the one which best serves the interests and needs of the medical community. We would, of course, be happy to discuss remaining questions or issues concerning the package label or any other issue related to the Bravelle™ NDA with FDA.

Sincerely,

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

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

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LABELING-Package Insert
Revised Text
Final Text
FAX 6/5/01

FERRING
PHARMACEUTICALS

May 24, 2001

DUPLICATE

Susan Allen, 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

NDA ORIG AMENDMENT
BM

RE: OVANEX, NDA 21,289 Amendment #013

Dear Dr. Allen:

Enclosed please find Amendment #013 to NDA #21,289. This amendment provides revisions to the package insert. Specifically, revisions are included to the:

- Warning Section concerning OHSS, and
- Table 7 – Patients with Adverse Events

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

Sincerely,

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

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

DUPLICATE

May 15, 2001

Susan Allen, 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

ORIG AMENDMENT
BC

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 16 2001
HFD-580

Re: NDA 21-289, Ovanex™ (urofollitropin for injection)
Amendment No. 012

Dear Dr. Allen:

Enclosed please find our response to the request from Dr. Rhee in the Information Request Letter of May 11, 2001, which also referred to our responses dated January 24 and February 9, 2001 regarding the endotoxin specification for the drug product. Dr Rhee requested that we "**provide the new final product —— specification for this drug product.**"

> **The new specification for the drug product is —— units per FSH unit.**
>
> At the maximum labeled dose of 450 IU FSH this allows no more than 4.5 EU/kg/hr (based on a 70 kg adult) —— per IU FSH multiplied by 450 IU FSH = —— or —— for a 70 kg adult. This is within the maximum recommended —— dose per Dr. Rhee's letter of January 24, 2001 of —— (based on a 70 kg adult) or a maximum of ——
>
> Please refer to our NDA amendment 006, April 5, 2001, in which we submitted a revised drug product specification (Volume 4K page 167). **The —— specification is ' —— units per FSH unit".** A copy of this specification is enclosed for your convenience.

If you have any questions please feel free to contact me at (914) 333-8932.

Sincerely,

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

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

May 14, 2001

~~ORIGINAL~~
DUPLICATE

Susan Allen, 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

BS
NDA ORIG AMENDMENT

RE: OVANEX, NDA 21,289 Supplement #011

Dear Dr. Allen:

Ferring is submitting this supplement to NDA #21-289 in response to a telephone query from Dr. David Hoberman, Mathematical Statistician, ORM, DOBII concerning study FPI FSH 99-03 (Ovulation Induction). The submission consists of the following:

- Introduction and Tabular Summary of Pharmacological Responses
- Photocopy of the Section 11.d. (Efficacy Results) from Volume 8A (original NDA submission) pages 43-51, which describe comparative results for the primary and secondary efficacy variables by Treatment Group.
- Photocopies of the data listings from Volume 8E (original NDA submission), Appendix 17E, Data Listing 17, pages 228-233, which detail the patients hCG and post hCG response status by Treatment Group.

These documents show that there were two main reasons for patients not receiving hCG. One was inadequate response in terms of the protocol specified criterion of at least one follicle ≥ 14 mm. Four of the ten FSH SC patients, 6 of the 9 FSH IM patients and one of the 3 Follistim patients (total=11 patients) did not get hCG because of this. The second reason was risk of OHSS as perceived by the investigator. This clinical judgment was sometimes based on high E_2 levels, sometimes on numerous small to moderate sized ovarian follicles on transvaginal ultrasound and sometimes on both. None of these patients had any clinical evidence of OHSS and some clinical decisions not

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to give hCG were hyperconservative and based on the desire to avoid any risk of possible multiple pregnancies. Five of the 10 FSH SC patients, 2 of the 9 FSH IM and 2 of the 3 Follistim patients (total=9) did not get hCG because of this. Additionally, one FSH SC patient chose to discontinue after 8 doses even though she met criteria for receiving hCG because of personal not medical reasons and one FSH IM patient was discontinued because of investigator error even though she met hCG criteria.

There were approximately equal numbers of patients not getting hCG for reasons representing opposite poles of pharmacological response, i.e., inadequate response vs. risk of OHSS. This indicates these results constitute biological fluctuations typical of this therapeutic area and study size and do not represent meaningful pharmacological differences.

Ferring agrees with FDA's decision to designate ovulation as the primary efficacy variable because it is the most clinically relevant and important. As the study report efficacy section, included in this submission indicates, the ovulation rates across the 3 treatment groups on both intent-to-treat and primary efficacy responder analyses were numerically close and not statistically significantly different. Of interest was that although a higher percentage of Follistim patients met hCG criteria and received hCG, of those receiving hCG, higher percentages of FSH SC (25 of 26 = 96.2%) and FSH IM (26 of 28=92.9%) ovulated compared to Follistim (30 of 35=85.7%). It is likely that these differences derive from the same biological fluctuation causing the met hCG criteria and received hCG differences.

Also shown in the study report efficacy section is that all secondary efficacy variable were not statistically different across the treatment groups.

Finally, there were no adverse dropouts in this study and no patient failed to receive hCG because of an actual adverse event. We trust that this submission fully addresses your stated question.

Please contact us with any additional questions.

Sincerely,

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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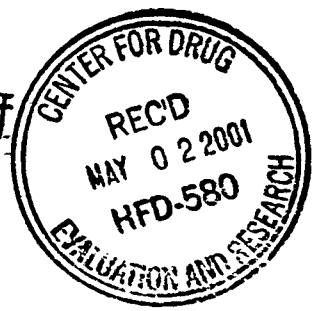
May 1, 2001

DUPLICATE

NDA ORIG AMENDMENT
BS



Susan Allen, 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: OVANEX, NDA 21,289 Supplement #010

Dear Dr. Allen:

Enclosed please find selected, consolidated SAS data sets on diskette containing primary and secondary efficacy assessments linked to patient randomization numbers, treatment group, study site, age and body mass index for studies FPI FSH 99-03 and 99-04. These consolidated, electronic SAS data sets were requested by Dr. David Hoberman, Mathematical Statistician, ORM, DOBII.

Please feel free to contact me with any further questions.

Sincerely,

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

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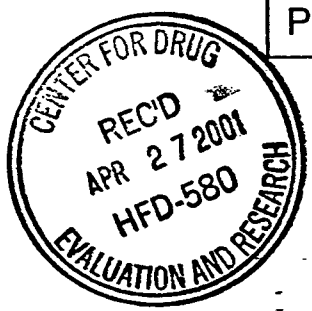
April 25, 2001



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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: CVANEX, NDA 21,289 Supplement #009

Dear Dr. Allen:

Enclosed please find Supplement #009 to NDA #21,289. Ferring recently submitted Amendment # 007 with revised packaging and labeling. The current submission consists of a correction of the package insert submitted in the Amendment # 007. The listed Parameter on line 5 of Table 4 (Pts. w/Chemical Pregnancy (%)) has been changed from ——— . Table 4 uses the entire sample of 30 recipient patients (Intent to Treat) who were prepared for embryo transfer. One of these patients did not receive embryo transfer because of microbial contamination of the eggs fertilized in vitro. In the tables in the full study report, the results are displayed using a denominator of 29, representing recipients who received embryo transfer.

Please feel free to contact me with any further questions.

Sincerely,

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

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April 23, 2001

ORIGINAL

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REC'D
APR 24 2001
HFD-580
EVALUATION AND RESEARCH

Re: NDA 21-289, Ovanex™ (urofollitropin for injection)
CMC Amendment
Amendment No. 008

ORIG AMENDMENT

BC

Dear Dr. Allen:

Enclosed please find four copies of the Methods Validation Volume for this NDA, Volumes 4F1 and 4F2. These volumes contain the methods validations that were included in the original submission and the following additional methods validations:

Drug Substance

[redacted]

Drug Product

[redacted]

The volume is organized by drug substance and drug product. A table of contents is provided. Where available, validation protocols and test methods are also included.

If you have any questions please do not hesitate to call me at (914) 333-8958.

Sincerely,

MBernhard

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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April 20, 2001

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Director
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Food and Drug Administration
5600 Fishers Lane
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ORIG AMENDMENT

DL

RE: NDA # 21-289 Ovanex™ (urofollitropin for injection), Amendment
FSH (urofollitropin)

Dear Dr. Allen,

Enclosed please find a labeling amendment to the above referenced New Drug Application (NDA #21-289). This amendment contains

- Revised package insert reflecting the change in trademark from Ovanex™ to Bravelle™. This change is being made to avoid conflicts that recently surfaced with the Ovanex™ trademark.
- Layout for the cartons for Bravelle™.
- Labels for the Bravelle™ vial.

Please note that the labeling revisions were made to the version of the package insert submitted on March 1, 2001. Replacing Ovanex with the Bravelle name is the only change in this revision.

We believe that this amendment addresses the request for packaging layout and color previous made by the agency. 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 #21-289

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April 5, 2001

ARCHIVE

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Director
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Office of Drug Evaluation II
Center for Drug Evaluation and Research
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5600 Fishers Lane
Rockville, MD 20857

RE: NDA # 21-289 Ovanex™ (urofollitropin for injection), Amendment 006
———— , FSH (urofollitropin)

Dear Dr. Allen,

Enclosed please find a CMC amendment to the above referenced New Drug Application (NDA #21-289). This amendment provides updated information on several CMC issues.

- Per the request of the FDA at the pre-NDA meeting, the sequencing of the FSH heterodimer has been completed. As suggested by the partial sequence data previously submitted, the sequences of the α- and β- chain are identical to the known sequences for these human proteins. Separate reports for the individual proteins are contained in this submission.
- The carbohydrate report has been updated to include information on the structure of the carbohydrate side chains.
- A report on the continuing characterization of the impurities is included. The data indicate that the impurities peaks previously identified contain several ———— . Each is present in small quantity (————). Efforts to identify individual ———— have not been successful to date.
- Stability data from recent time points are included to both drug substance and drug product. The overall stability data analyses are also updated in light of these additional data. A specification table for stability samples has been added
- Updated specification tables are provided for drug substance and reference standard and drug product. Several specifications were tightened based on additional data accumulated since the original submission.

Please note in the stability section that amended protocols are included. Tests that were not informative have been eliminated form future testing

Please note that the amendment uses the outline and Table of Contents format of the original NDA. This volume is identified as the next volume in section 4 (4K). The reports and stability data updates are identified based on their location in the overall outline of the CMC section.

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We are providing a copy of this amendment to the local inspection branch. Please note that a volume of validation reports is also in preparation for the inspection division. Please let us know if additional copies are needed.

We believe that this amendment completes all outstanding CMC issues raised at the pre-NDA meeting or during the review to date. 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 #21-289 Amendment 005

APPEARS THIS WAY
ON ORIGINAL