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# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 21-484

## Medical Review(s)

**Bravelle™ (urofollitropin for injection, purified)**
**Ferring Pharmaceuticals, Inc.**
**NDA 21-484**

## Safety Update Review

Please refer to the Medical Officer's review.

AM 12/05/02

Medical Officer's Original Clinical Review

NDA Number: 21-484 Name of Drug: Bravelle™

Applicant: Ferring Pharmaceuticals, Inc.

120 White Plains Road, Suite 400

Tarrytown, New York 10591

Date of Submission: February 15, 2002

Date Submission Received: February 19, 2002

Date Review Completed: October 31, 2002

**EXECUTIVE SUMMARY:**

I. Recommendations:

A. Approval of this application is recommended from a clinical perspective based on the acceptable demonstration of safety and efficacy in one pivotal clinical trial when the drug is administered subcutaneously (S.C.) to stimulate ovarian follicle development leading to retrieval of multiple oocytes in Assisted Reproductive Technology (ART) regimens and pregnancy. The benefit to risk ratio is favorable.

B. Phase 4 studies are not required. However, the applicant will complete two post marketing studies involving mixed treatment regimens of Bravelle™ and Repronex® in patients undergoing IVF cycles, for its own purposes.

II. Summary of Clinical Findings:

A. Brief Overview of Clinical Program:

1. Name of Product: Bravelle™ (purified urofollitropin)

2. Therapeutic Class of Product: Infertility

3. Routes of Administration: S.C. and I.M.

4. Clinical Trial: The results of one multicenter, randomized trial comparing Bravelle™ S.C., and Follistim® S.C. in 120 subjects undergoing in-vitro fertilization (IVF) are submitted.

B. Efficacy: Efficacy was demonstrated for multiple follicular development (controlled ovarian stimulation) during ART cycles in patients who have previously received pituitary suppression.

For the IVF study, the primary efficacy variable of oocytes retrieved per person showed no statistically significant differences in either the intent-to-treat (ITT) or primary efficacy responder (received hCG) populations between Bravelle™ S.C., and Follistim® S.C

The efficacy when Bravelle is administered S.C. is the same as that reported for other drugs marketed for the same indications.

C. Safety: Safety testing is adequate. Each subject was treated for one cycle for a maximum of 12 days. Monitoring and follow-up were adequate. The most significant adverse effect was the development of the ovarian hyperstimulation syndrome (OHSS). During ART treatment, OHSS occurred in 3 Bravelle™ treated subjects including 1 serious case requiring hospitalization. OHSS is recognized as the most serious adverse event occurring with the use of gonadotropins in infertility treatment and is adequately addressed in the proposed labeling for this product.

No drug/drug interaction studies have been conducted for Bravelle™ in humans. However, it is well known that hCG can make the occurrence of OHSS worse and the labeling clearly states that usually, in cases where OHSS may be developing prior to hCG administration, hCG should be withheld. If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized. A physician experienced in the management of OHSS or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

Subjects with an active or prior history of substance abuse, including alcohol and tobacco, were excluded from the clinical trials, except for subjects who stopped tobacco usage at least 3 months prior to baseline visit. It is expected that when the drug is marketed, smokers may also be treated with it. This should not result in any significant increased risk to those smokers.

The warnings in the labeling are adequate. The safety of this drug is the same as that for other drugs used for the same indication.

There are no unresolved safety issues.

D. Dosing: The dosage and administration are the same as that utilized in similar drug products that have had a good safety record over years of marketing. The effects of dosing are closely monitored by the use of vaginal ultrasound and serum estradiol levels. There are no dose modifications recommended and there are no unresolved dosing/administration issues.

E. Special Populations: This drug is being approved for conditions that occur only in women. The drug is not indicated for use in pediatric patients and safety and efficacy in such patients have not been established. Clinical studies did not include subjects over the age of 39 years. This drug is contraindicated in pregnancy. The safety and efficacy of the drug in renal and hepatic insufficiency have not been studied. The vast majority of subjects in the trial (82% -87%) were Caucasian with about 7%-10% African-Americans. Racial and ethnic differences are not likely to be of any significant concern regarding efficacy or safety of the drug product.

CLINICAL REVIEW:

I. Introduction and Background:

A. Established Drug Name: Purified urofollitropin

B. Proposed Trade Name: Bravelle™

C. Therapeutic Class: Infertility

D. Indication: Bravelle™ in conjunction with hCG, is indicated for multiple follicular development (controlled ovarian stimulation) during ART cycles.

E. Dosage:

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

Once adequate follicular development is evident, hCG (5000-10,000 USP units) should be administered on the day following Bravelle™ to induce final follicular maturation.

F. Age Groups Studied: 18-39 years of age.

G. Brief Overview of Clinical Study: The NDA includes one controlled study (FPI FSH 2001-01 in patients undergoing IVF which constitutes the

pivotal efficacy trial. The study had a randomized, open label, assessor-blind, parallel group, multi-center design comparing Bravelle™ S.C. and Follistim® S.C.

H. Armamentarium for Indication: There are many drugs already marketed for this indication.

I. Prior FDA Reviews and Issues: At the pre NDA meeting April 24, 2000, the applicant was informed that the Division does not view study 99-05 as adequate to support labeling for use of Bravelle™ in donor IVF programs. The applicant agreed with this assessment.

J. Foreign Marketing Status: Bravelle™ has not been marketed in any country.

II. Clinically Relevant Findings from Pharmacology Studies: Bravelle™ is a highly purified preparation of urofollitropin extracted from the urine of post-menopausal women. It contains 75 IU of FSH biological activity and 1-2% of LH biological activity in each vial based on the WHO validated rat bioassay used as a release test for all gonadotropin drug products, according to the applicant.

Because gonadotropins including urofollitropins and recombinant follitropins have been approved and extensively used as fertility treatments for oligoanovulatory patients and patients undergoing *in vitro* fertilization, the clinical program for Bravelle™ did not include pharmacology studies in humans.

III. Human Pharmacokinetics and Bioavailability: Single and multiple dose (7 daily doses) studies of Bravelle™ administered S.C. and I.M.were conducted in normal healthy female subjects. Sixteen subjects were evaluated for S.C. administration followed by twelve subjects for I.M. administration. The sample size for the I.M. group was reduced from 16 to 12 after analysis of the S.C. results demonstrated sufficient intersubject consistency to allow an accurate determination of classical PK parameters with the smaller number of subjects. The formulation used in these studies was a sterile, lyophilized powder containing 75 IU of FSH activity, plus 20 mg of lactose as the monohydrate, 0.005 mg tween, sodium phosphate buffer (sodium tribasic and phosphorus acid), and 1-2 % of leuteinizing hormone activity. This formulation is identical to the planned commercial formulation. Over all, S.C. administration appeared to provide slightly higher AUC and Cmax than I.M. administration.

IV. Description of Clinical Data and Sources:

A. Overall Data: The data are from the clinical trial program conducted exclusively at private practice centers specializing in fertility treatment. All principal investigators were reproductive endocrinologists.

B. Disposition of Subjects: Treatment was for one cycle and the maximum duration of treatment was 12 days.

In the IVF study, 130 subjects were enrolled and started on leuprolide acetate for down regulation. Ten of these subjects were not randomized because they did not achieve down regulation, they were pregnant, or for other reasons. A total of 120 subjects were randomized and all were evaluable for safety and efficacy in the intent-to-treat analyses.

C. Postmarketing Experience: None

D. Literature Search: None

V. Clinical Review Methods:

A. Description of How Review was Conducted: The one pivotal study was reviewed in entirety.

B. IND Evaluation: IND( )was reviewed in detail. The clinical protocol was originally submitted to the IND, where it was evaluated and found to be acceptable.

C. Data Quality and Integrity: The Division of Scientific Investigations audited some investigators.

D. Ethical Issues: The informed consent documents were satisfactory.

E. Financial Disclosure: The sponsor provided appropriate documentation for financial disclosure information for all investigators. There was no disclosure of financial interests that could bias the outcome of the clinical trials.

VI. Review of Efficacy:

A. Findings in Light of Proposed Labeling Claims: Study 2001-01 supports the claim of multiple follicular development (controlled ovarian stimulation) when Bravelle™ is administered S.C. in patients who have previously received pituitary suppression.

B. Integrated Summary of Efficacy: Efficacy results for one randomized, active controlled, multi-center study in IVF are summarized in Table 1. The patients underwent pituitary suppression with a GnRH agonist before staring Bravelle™ administration. The study evaluated 120 patients undergoing IVF who received 225 IU Bravelle™ daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol levels. The total duration of dosing did not exceed 12 days.

On the intent-to-treat analysis, the 95% CI mean (two tailed) for oocytes retrieved was 10.1 to 13.4 for Bravelle™ and 10.1 to 13.7 for Follistim® with a potential lower-bound difference form Follistim SC (one-tailed) of –2.1 using one-way ANOVA and –2.3 using adjusted means from ANCOVA with age and BMI as covariates. The unadjusted ANOVA based confidence interval calculation was the primary analysis.

Table 1

(Sponsor's Tables 4 and 6, Vol. 8A)

Efficacy Outcome by Treatment Group for IVF (Intent to Treat)

| | Bravelle™ SC | Follistim® SC |
|---|---|---|
| Parameter | N=60 | N=60 |
| Total oocytes Retrieved per Patient (SD) | 11.8 (6.3) | 11.9 (6.9) |
| Mature oocytes Retrieved per Patient (SD) | 9.0 (5.7) | 9.2 (6.0) |
| Pts w/oocyte Retrieval (%) | 57 (95.0) | 59 (98.3) |
| Pts w/Embryo Transfer (%) | 57 (95.0) | 58 (96.7) |
| Pts w/Chemical Pregnancy (%) | 28 (46.6) | 30 (50.0) |
| Pts w/Clinical Pregnancy (%) | 25 (41.7) | 27 (45.0) |
| Pts w/Continuing Pregnancy (%) | 23 (38.3) | 27 (45.0) |

The primary efficacy variable, total oocytes retrieved per patient, showed no clinically or statistically significant differences between Bravelle™ S.C. and Follistim® S.C.

C. Statistician's Evaluation: Please refer to statistician's review.

VII. Integrated Review of Safety:

A. Findings as Reflected in Proposed Labeling: Safety is based on the data from study 2001-01 as well as studies 99-03 and 99-04 with the additional data from a small (30 patients), uncontrolled donor egg study (study 99-05). Each subject was treated for one cycle for a maximum of 12 days. Monitoring and follow-up were adequate. The most serious adverse effect was the development of OHSS. During ART treatment, OHSS occurred

in 12 Bravelle™ treated subjects including 4 serious cases requiring hospitalization. During ovulation induction, OHSS occurred in 6 Bravelle™ treated subjects including 2 serious cases. Most cases were associated with early pregnancy. OHSS occurred in 6.4% of Bravelle™ treated subjects and 4.5% of Follistim® treated subjects. Adverse events by body systems are accurately detailed in the draft labeling.

B. Patient Exposure and Safety Assessment: Patients were treated for one cycle and for a maximum of 12 days. All adverse events, whether or not felt to be related to Bravelle™, were tabulated and are detailed in the draft labeling. The drug is safe, based on the reported adverse events. Patient exposure was adequate and the safety profile for Bravelle™ has been adequately defined.

C. Specific Findings of Safety Review: There were no deaths or adverse dropouts in the studies.

Pain on injection was assessed by each patient on each day of follitropin treatment using a digital scale numbered 1 through 10, with 1 being no symptoms and 10 being severe pain.

In the ovulation induction study, reviewed in NDA 21-289, there were no statistically significant differences in mean injection site pain score on any day of treatment or for the cumulative mean, Days 1 to 12. Pain scores were generally in the mild range and no patient interrupted or discontinued treatment because of local intolerance to the injection whether given S.C. or I.M.

In the IVF studies 99-04 and 2001-01, the applicant concluded that Bravelle™ administered S.C. or I.M. demonstrated clinically meaningfully better local tolerance with less injection site pain and irritation than Follistim® S.C. The difference was related to the difference in Polysorbate 20 concentrations, according to the applicant. However, if this were true, one would expect to have found the same difference in the ovulation induction study. Such a difference was not found even though both studies were conducted during the same time frame and with the same differences of Polysorbate 20 in the Bravelle™ and Follistim®. Therefore, one cannot determine that there is, in fact, a real difference in local tolerability favoring Bravelle™ over Follistim®.

VIII. Assessment of Dosing/Regimen/Administration Issues: The dosage and administration are the same as that utilized in similar drug products that have had a good safety record over years of marketing. The effects of dosing are closely monitored by the use of vaginal ultrasound and serum estradiol levels. There are no dose modifications recommended and there are no unresolved dosing/administration issues.

IX. Use in Special Populations:

A. This drug is being approved for conditions that occur only in women.

B. This drug is not indicated for use in pediatric patients and safety and efficacy in such patients have not been established.

C. The vast majority of subjects in the trial (82%-87%) were Caucasian with about 7%-10% African-Americans. Racial and ethnic differences are not likely to be of any significant concern regarding efficacy or safety of the drug product.

D. Clinical studies did not include subjects over the age of 39 years. This drug is contraindicated in pregnancy. The safety and efficacy of the drug in renal and hepatic insufficiency have not been studied.

X. Conclusions and Recommendations:

A. Overall Risk-Benefit Analysis: The clinical study described in this NDA document the therapeutic efficacy and safety of Bravelle™ administered S.C. to stimulate ovarian follicle development leading to retrieval of multiple oocytes in ART regimens and pregnancy.

Given the long history of efficacy and safety in clinical practice of follitropins and the good results for Bravelle™ obtained in the clinical study reported in this NDA, the benefit to risk relationship of Bravelle™ S.C. is favorable for ART regimens.

The benefits of the drug outweigh its risks.

B. Remaining Unresolved Issues: None.

C. Summary of Major Issues Regarding Draft Package Insert:

1. The applicant included efficacy results from a small, non-randomized, open-label, single treatment arm, study of Bravelle™ SC to stimulate multiple follicle development in donor egg patients. The patient population in this study was different from the IVF clinical study. These patients were healthy, younger women with lower body mass index than those in the IVF clinical study. At the pre NDA meeting April 24, 2000, the applicant was informed that the Division does not view this study as adequate to support labeling for use of Bravelle™ in donor egg programs. The applicant agreed with our assessment. The applicant was asked to remove [redacted] However, it remains in the draft labeling submitted.

2. The applicant was asked [redacted], but to report the outcome of pregnancies from the IVF study only, [redacted] However, combined pregnancy rates remain in the draft labeling submitted.

3. The applicant was asked to include OHSS as a possible adverse reaction to be discussed with the patient prior to therapy with Bravelle™. However, this does not appear in the draft labeling submitted.

4. The applicant was asked to delete [redacted] However, it is still present in the draft labeling submitted.

5. The applicant was asked to revise the indication to indicate that Bravelle™ was indicated for multiple follicular development during ART cycles. However, this does not appear in the draft labeling submitted.

D. Approval of this application is recommended for S.C. administration of Bravelle™ for ARTregimens.

E. Post-Marketing Risk Management Studies Recommended: None.

XI. Individual Study Review , Protocol 2001-01:

A. Title of the Study: A Randomized, Assessor-Blind, Parallel Group, Multi-Center Efficacy Study in Comparing Purified FSH S.C., and Follistim® S.C. in Female Patients Undergoing In-Vitro Fertilization.

B. Investigators and Study Sites:

| | |
|---|---|
| Paul Katayama | Milwaukee, WI |
| Jack Crain | Charlotte, NC |
| Richard Dickey | New Orleans, LA |
| Benjamin Gocial | Plymouth Meeting, PA |
| John Nichols | Greenville, SC |
| Michael Steinkampf | Birmingham, AL |
| Michael Kettel | San Diego, CA |
| Paul Magarelli | Colorado Springs, CO |
| Sam Najmabi | Valencia, CA |
| Grant Patton | Mt. Pleasant, SC |
| Stephen Somkuti | Abington, PA |
| Bobby Webster | Baton Rouge, LA |
| Timothy Yeko | Tampa, FL |

C. Objectives of the Study: To determine the therapeutic efficacy of purified FSH S.C. compared to Follisitim® S.C. in terms of number of oocytes retrieved, percentage cycles with oocyte retrieval, and percentage cycles with pregnancy.

To determine the safety and tolerance of purified FSH S.C. compared to Follistim® S.C.

D. Rationale for the Study: Various urofollitropin and recombinant FSH products have been approved for treatment of anovulatory and

oligoovulatory female infertility. This study was conducted to evaluate and compare the therapeutic efficacy and safety in patients undergoing I.V.F. of purified FSH S.C. and Follistim®, an approved product for this indication.

E. Method of Assignment to Treatment: Subjects were randomly assigned to receive one of the two treatments using a randomization code.

F. Number of Subjects: A total of 130 subjects were enrolled and started on leuprolide acetate for down regulation. Ten of these subjects were not randomized to follitropin because they failed to down regulate to estradiol, $\leq 45$ pg/mL and endometrial lining $\leq 7$ mm on transvaginal ultrasound, they were pregnant, or for other reasons, A total of 120 subjects were randomized to follitropin terapy and all were evaluable for efficacy and safety in the intent-to-treat analysis.

G. Duration of Treatment: One cycle, maximum treatment of 12 days.

H. Inclusion Criteria: Subjects were eligible for enrollment in the study if they met all of the following criteria:

(1) Signed Informed Consent Form, prior to screening evaluations.

(2) Nonsmoking females between the ages of 18 and 39 years (treatment initiation must have taken place before reaching 40$^{th}$ birthday) and premenopausal.

(3) Regular, ovulatory menstrual cycles of 24-35 days and documented evidence of at least one of the following:

- mid-luteal phase serum Progesterone level > 5ng/mL, or
- late luteal phase endometrial biopsy with < 3 days lag, or
- biphasic basal body temperature chart, or
- history of mid-cycle urinary LH surge within one of the past two (2) cycles.

(4) Early follicular phase (day 2-3, preferably day 3) serum $E_2$, FSH, PRL, T, DHEA-S and TSH levels within the normal limits for the clinical laboratory, or considered not clinically significant by investigator. These tests had to be performed within sixty (60) days of entry into the study (start of leuprolide acetate treatment).

(5) Clinically normal baseline hematology, clinical chemistry (SMA-24), and urinalysis parameter values, negative serum hepatitis B surface antigen, negative hepatitis C antibody, negative human immunodeficiency virus (HIV) antibody and negative rapid plasma reagin tests within 60 days prior to leuprolide acetate treatment.

(6) Seropositive for rubella and varicella prior to leuprolide acetate.

(7) Infertility attributable to or in association with either tubal factors, endometriosis (stage I or II only), or unexplained causes. Couples with an associated male factor could be enrolled only if donor sperm was to be used.

(8) Male partner with recent (within previous six months) semen analysis. If screening semen analysis was borderline, the couple could be accepted into the study if a second sample obtained was adequate. Donor sperm could be used, if indicated.

(9) Presence of both ovaries, without evidence of abnormality, as detected by vaginal ultrasound performed prior to study enrollment.

(10) Normal transvaginal ultrasound with respect to uterus and adnexae (no hydrosalpinges, no uterine fibroids).

(11) A minimum of one cycle without treatment with fertility modifiers immediately prior to screening.

(12) A minimum of one cycle without IVF/ART treatment immediately prior to screening.

(13) Hysterosalpinography, hysteroscopy, or sonohysterogram documenting a uterine cavity consistent with expected normal function within the previous three (3) years prior to the baseline visit.

(14) Negative serum pregnancy test (qualitative) prior to beginning therapy (pre-leuprolide acetate).

(15) Desire to become pregnant.

I. Exclusion Criteria: The study enrolled patients who did not exhibit any of the exclusion criteria listed below:

(1) Presence of any clinically relevant systemic disease (e.g., insulin-dependent diabetes mellitus).

(2) Surgical or medical condition which in the judgment of the Investigator or Sponsor would interfere with absorption, distribution, metabolism, or excretion of the drugs used.

(3) Any pregnancy within last three months prior to screening.

(4) A body mass index of greater than 34.

(5) More than three previous ART cycles.

(6) Previous IVF or ART failure related to either a sperm/fertilization problem which resulted in unsuccessful fertilization or an ART with a poor response to gonadotropins. Poor response was defined as development of $\leq 2$ mature follicles or history of two previous cycle cancellations prior to oocyte retrieval due to poor response.

(7) Presence of abnormal uterine bleeding of undetermined origin.

(8) Active or prior history of substance abuse, including alcohol and tobacco (Patients who had discontinued tobacco use at least three months prior to the baseline visit would be allowed).

(9) History of chemotherapy (except for gestational conditions) or radiotherapy.

(10) Breast feeding, or pregnant at screening or had any contraindication to pregnancy.

(11) Refused or was unable to comply with the requirements of the Protocol for any reason, including scheduled clinic visits and laboratory tests.

(12) For male partner, obvious leukospermia (> 2 million WBC/mL) or signs of infection in semen sample within past two months; if either of these conditions existed, male could be treated with

antibiotics and retested prior to his spouse receiving leuprolide acetate.

(13) Documented intolerance or allergy to any gonadotropin or follitropin product.

(14) Participated in any experimental drug study within the sixty days prior to screening for this study.

J. Trial Period: September 17, 2001 to January 19, 2002

K. Dosage and Mode of Administration: The assigned follitropin was administered S.C. as a single daily dose of 225 IU for 5 days after which doses were individualized to a maximum daily dose of 450 IU for a total duration not exceeding 12 days.

L. Primary and Secondary Efficacy Assessments:

Table 2

(Sponsor's Tables 4 and 6, Vol. 8A)

Efficacy Outcome by Treatment Group for IVF (Intent to Treat)

| | Bravelle™ SC | Follistim® SC |
|---|---|---|
| Parameter | N=60 | N=60 |
| Total oocytes Retrieved per Patient (SD) | 11.8 (6.3) | 11.9 (6.9) |
| Mature oocytes Retrieved per Patient (SD) | 9.0 (5.7) | 9.2 (6.0) |
| Pts w/oocyte Retrieval (%) | 57 (95.0) | 59 (98.3) |
| Pts w/Embryo Transfer (%) | 57 (95.0) | 58 (96.7) |
| Pts w/Chemical Pregnancy (%) | 28 (46.6) | 30 (50.0) |
| Pts w/Clinical Pregnancy (%) | 25 (41.7) | 27 (45.0) |
| Pts w/Continuing Pregnancy (%) | 23 (38.3) | 27 (45.0) |

On the intent-to-treat analysis, the 95% CI mean (two tailed) for oocytes retrieved was 10.1 to 13.4 for Bravelle™ and 10.1 to 13.7 for Follistim with a potential lower-bound difference from Follistim SC (one-tailed) of –2.1 using one-way ANOVA and –2.3 using adjusted means from ANCOVA with age and BMI as covariates. The unadjusted ANOVA based confidence interval calculation was the primary analysis.

M. Safety Assessment: There were no deaths or adverse dropouts in this study. Two serious adverse events occurred in one subject.

Pain on injection was assessed by each patient on each day of follitropin treatment using a digital scale numbered 1 through 10, with 1 being no symptoms and 10 being severe pain.

In the study, the applicant concluded that Bravelle™ administered S.C. demonstrated clinically meaningfully better local tolerance with less injection site pain and irritation than Follistim® S.C. The difference was related to the difference in Polysorbate 20 concentrations, according to the applicant. However, if this were true, one would expect to have found the same difference in the ovulation induction study. Such a difference was not found even though both studies were conducted with the same differences of Polysorbate 20 in the Bravelle™ and Follistim®. Therefore, one cannot determine that there is, in fact, a real difference in local tolerability favoring Bravelle™ over Follistim®.

N. Disposition of Patients: A total of 130 subjects were enrolled and started on leuprolide acetate for down regulation. Ten of these subjects were not randomized to follitropin because they failed to down regulate to estradiol $\leq$ 45 pg/mL and endometrial lining < 7mm on trangsvaginal ultrasound, they were pregnant, or for other reasons. A total of 120 subjects were randomized to follitropin therapy and all were evaluable for efficacy and safety in the intent-to-treat analysis.

O. Protocol Violations: Numerous minor protocol deviations occurred during the conduct of this study. Most did not affect the evaluability of the patients and were related to small exceptions prospectively made by Ferring for such things as semen analysis, $E_2$ levels and the timing of screening procedures.

P. Demographic Characteristics: Overall, the subjects in both treatment groups were comparable demographically and medically.

Q. Reviewer's Comments: **This study was conducted generally along the lines that other urofollitropins have followed. It was a one cylce study in down regulated subjects who met all of the inclusion criteria and had none of the exclusion criteria. Sample size and statistical methodologies were agreed upon before the study began by the applicant and FDA.**

**FSH S.C. was at least equal in effectiveness to Follistim® S.C. in terms of primary and secondary efficacy variables assessed in this study.**

**Both treatments showed excellent safety profiles with no dropouts due to adverse events.**

**The applicant concluded that Bravelle™ administered S.C. demonstrated clinically meaningfully better local tolerance with less injection site pain and irritation than Follistim® S.C. The difference was related to the difference in Polysorbate 20 concentrations, according to the applicant. However, if this were true, one would expect to have found the same difference in the ovulation induction study. Such a difference was not found even though both studies were conducted with the same differences of Polysorbate 20 in the Bravelle™ and Follistim®. Therefore, one cannot determine that there is, in fact, a real difference in local tolerability favoring Bravelle™ over Follistim®.**

**Bravelle™ administered S.C. is a safe and effective drug for use in patients undergoing in vitro fertilization. However, its efficacy for multiple follicular development in an ART regimen when administered I.M. has not clearly been established.**

/S/

Ridgely C. Bennett, M.D., M.P.H.

Medical Officer, HFD-580

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

/s/
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Ridgely C. Bennett
10/31/02 07:35:25 AM
MEDICAL OFFICER

Ridgely C. Bennett
10/31/02 07:36:37 AM
MEDICAL OFFICER

Shelley Slaughter
12/17/02 12:49:06 PM
MEDICAL OFFICER
I concur with Dr. Bennett's recommendation for approval. See also TeamLeader Memorandum.

**Bravelle™ (urofollitropin for injection, purified)**
**Ferring Pharmaceuticals, Inc.**
**NDA 21-484**

## Safety Update Review

The safety update review is part of the clinical review of this new drug application.

cm 12/08/02