CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 21047

MEDICAL REVIEW(S)

MEDICAL OFFICER'S NDA REVIEW

NDA Number: 21,047

Applicant: Ferring Pharmaceuticals Inc.
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Dates of Submissions: October 26, 1998 and March 24, 1999

Dates Received: October 28, 1998 and March 26, 1999

Date Review Completed: July 28, 1999

Date Review Revised: August 7, 1999

Date Review Finalized: August 7, 1999

I. General Information:

A. Name of Drug:

1. Established Name: Menotropins for Injection

2. Trade Name: Repronex

3. Chemical Name: Extract of Human Postmenopausal Urine Containing Follicle Stimulating Hormone and Luteinizing Hormone

B. Pharmacologic Category: Gonadotropins

C. Proposed Indications: Induction of ovulation and pregnancy in the anovulatory infertile patient, in whom the cause of anovulation is functional and is not due to primary ovarian failure and to stimulate the development of multiple follicles in ovulatory patients participating in an in vitro fertilization program.

D. Dosage Form and Routes of Administration: Lyophilized powder or pellet in vials for reconstitution for subcutaneous or intramuscular administration.

E. Strengths: Each vial contains 75 IU FSH and 75 IU of LH activity or 150 IU FSH and 150 IU of LH activity.

F. Dosage: The Dose of Repronex to produce maturation of the follicle must be individualized for each patient. The initial dose to any patient should be 75 IU if not downregulated and 150 IU if her pituitary function has been suppressed by a GnRH analog. After five days on this dosage, doses may be adjusted individually based on ultrasound findings and serum estradiol levels within a range of 75 IU to 450 IU per day for up to 7 additionai days (total dosing of up to 12 days) followed by hCG 5,000 U to 10,000 U one day after the last dose of Repronex.

G. Related Drugs: Pergonal and Humegon.
Repronex was approved for intramuscular administration under ANDA 73-598/599 and investigated for subcutaneous administration under IND

H. Active Ingredients: Follicle stimulating hormone and luteinizing hormone.

I. Prescription or O.T.C.: Prescription

II. Manufacturing Controls:

Please refer to chemist's review for details.

III. Pharmacology and Pharmacodynamics:

Please refer to pharmacologist's review for details.

IV. Clinical Background:

Repronex is a partially purified preparation of gonadotropin extracted from the urine of postmenopausal women. It contains equal amounts of FSH and LH activity. Repronex has been approved by FDA under ANDA 73-598/599 for intramuscular administration as being equivalent to Pergonal.

Menotropins have been used for decades in women without primary ovarian failure to induce ovarian follicle development for ovulation induction and in more recent years for oocyte retrieval in IVF procedures. The therapeutic class in which Repronex is clinically used is infertility.

The clinical benefits of menotropins are well established. Menotropins are approved for treatment of these specific causes of infertility when administered by the intramuscular route. This NDA is submitted to document the clinical efficacy and safety of Repronex subcutaneously for the same indications as those already

approved when the drug is administered intramuscularly.

V. Regulatory Background:

A. On July 3, 1996 Lederle Laboratories transferred ownership of ANDA 73-598 (menotropins) to Ferring Pharmaceuticals, Inc. Upon approval of the ANDA, Ferring Pharmaceuticals began commercial production of menotropins at the Lederle plant in Puerto Rico. Repronex is approved under ANDA 73-598 for induction of ovulation and for I.V.F. when administered by the intramuscular route.

B. IND was submitted August 14, 1997 to study Repronex for the clinical indications already approved, but when administered by the subcutaneous route.

C. A pre-NDA meeting was held with Ferring Pharmaceuticals March 10, 1998 to discuss the planned submission of an NDA for the administration of Repronex subcutaneously which would include the final results of the clinical studies conducted under IND

VI. Foreign Marketing History:

Ferring affiliates have marketed menotropins in Europe and the Middle East under the brand name of Menogon since June, 1993. produces the drug substance for both Menogon and Repronex. The production process for both products is the same except that the drug substance for Repronex has sodium phosphate buffer to control the pH in the range 6.0-7.0 added as a last processing step. Menogon has less lactose (5mg/vial) than Repronex (20mg/vial) in the finished product formulation. The manufacturing process is slightly different for Menogon and Repronex although the end products meet similar specifications. Potency testing uses the same analytical methods for both products.

VII. Consultation:

Please refer to statistician's review for details.

VIII. Clinical Studies:

The efficacy and safety of Repronex, subcutaneously, was evaluated in two completed, controlled, multicenter, randomized, parallel group clinical trials conducted in the United States. Under protocol 97-01, oligoovulatory infertile female subjects (most of whom had a diagnosis of polycystic ovary disease) were

evaluated and under protocol 97-02, female subjects undergoing IVF were evaluated. Under protocol 97-01, a subgroup of subjects were also evaluated for single and multiple dose pharmacokinetic parameters. Both protocols 97-01 and 97-02 compared Repronex subcutaneously with Repronex intramuscularly and Pergonal intramuscularly.

A. Study 97-01. A Randomized, Open-Label, Parallel Group, Multi-Center, Pharmacokinetic/Pharmacodynamic Study in Anovulatory and Oligoovulatory Infertile Female Patients Comparing Repronex S.C., Repronex I.M., and Pergonal I.M. for Ovulation Induction.

1. Investigators:

Jack Crain, Charlotte, NC
Benjamin Gocial, Philadelphia, PA
John Queenan, Jr., Mt. Pleasant, SC
Eric Knochenhauer, Birmingham, AL
William Kutteh, Memphis, TN
Milton McNichol, Houston, TX
Edward Moore, Columbia, SC
John Nichols, Greenville, SC
William Schlaff, Denver, CO
David Walmer, Durham, NC

2. Objectives of the Study:

Clinical objectives of the study were to determine the pharmacological efficacy and safety of Repronex S.C. compared to Repronex I.M. and Pergonal I.M.

3. Rationale for the Study:

Several menotropins have been approved for the induction of ovulation when administered intramuscularly. Subcutaneous administration may provide a more convenient and better tolerated treatment than intramuscular administration while providing comparable efficacy. A number of studies have evaluated the pharmacokinetics of S.C. and I.M. gonadotropins and documented that they are not bioequivalent routes of administration. Nevertheless, the systemic bioavailability of S.C. gonadotropins has been found to be good. This study was conducted to evaluate and compare the therapeutic efficacy and safety of Repronex S.C., Repronex I.M., and Pergonal I.M. in patients for ovulation

induction.

4. Method of Assignment to Treatment:

Patients were randomly assigned to receive one of the three treatments using a randomization code that yielded equal numbers of subjects in each treatment arm.

5. Number of Subjects:

A total of 115 patients were enrolled and started on down regulation with leuprolide acetate. One hundred eight successfully down regulated, were randomized to treatment with gonadotropin and were included in the analyses of efficacy and safety. Two patients were non-compliant with the leuprolide regimen and were lost to follow-up. Five patients failed to adequately down regulate.

6. Duration of Clinical Trial:

One treatment cycle only.

7. Inclusion Criteria:

a. Signed informed consent form
b. Nonsmoking females aged 18-39
c. Infertile due to ovulatory dysfunction
d. Anovulatory or oligoovulatory
e. Body mass index not greater than 38
f. Menses or progesterone withdrawal bleeding within 3 months
g. FSH and PRL within the normal range.
h. DHEA-S and T not exceeding >50% the upper limit of the normal range
i. Normal baseline hematology, chemistry, and urinalysis
j. Normal transvaginal ultrasound
k. Patency of at least one Fallopian tube
l. Normal uterine cavity
m. Normal semen analysis of partner
n. No treatment with fertility drugs within 1 month
o. Negative serum pregnancy test
p. Willingness to comply with the protocol
q. Desire to become pregnant

8. Exclusion Criteria:

a. Any condition that might interfere with the pharmacokinetics
b. Any clinically significant systemic disease
c. Medications that would interfere with study medications
d. Pregnancy within 3 months of screening
e. Previous treatment with gonadotropins
f. Ovarian cyst greater than 15mm in diameter
g. Clinically significant uterine fibroids
h. Abnormal bleeding
i. Active substance abuse by history
j. Tobacco use within 1 month of study entry
k. Stage III or IV endometriosis
l. History of chemotherapy or radiotherapy
m. Currently pregnant or breast feeding
n. Unable or unwilling to comply with the protocol
o. Intolerance or allergy to any gonadotropin
p. Participation in drug study within 60 days
q. Blood or plasma donation within 2 months

9. Trial Period:

March 3, 1998 - January 25, 1999

10. Dosage and Mode of Administration:

Patients were down regulated with leuprolide acetate 1 mg subcutaneously daily beginning on cycle day 2. If estradiol levels were not ≤ 30 pg/mL within 2 weeks, leuprolide was continued for a maximum of 20 days. Any patient who failed to down regulate within the 20 day time frame was discontinued from the study.

Once down regulation had occurred, patients continued leuprolide at the same daily dose and began the gonadotropin treatment to which they had been randomized within 3 days. Leuprolide was continued through the last day of gonadotropin dosing.

The starting doses of Repronex and Pergonal were originally 450 IU X 1 day followed by 225 IU x4 days after which doses were to be individualized within a range of 150 IU to 450 IU daily for a total duration not exceeding 12 days. Because of several cases of biochemical and ultrasound evidence of overstimulation by day 5, the protocol was amended to 150 IU x 5 days followed by

individualized dosing within a range of 150 to 450 IU daily for a total duration not exceeding 12 days.

A single dose of hCG 10,000 USP units I.M. was administered on the day following the last dose of gonadotropin if at least 1 follicle reached a diameter of 14mm or greater and the estradiol levels were appropriate for the number of follicles observed and did not exceed 3000 pg/mL.

11. Efficacy Assessments:

The primary efficacy variable was ovulation. The number and percentage of patients who ovulated was calculated, analyzed, and compared across the three treatment groups. Chi-squared tests and multiple logistic regression were utilized.

Secondary efficacy variables including percentage of patients meeting hCG criteria, number of follicles recruited per cycle meeting hCG criteria, peak serum estradiol levels, and percentage of patients with chemical, clinical, and continuing pregnancies were analytically handled in the same manner as the primary efficacy variable.

12. Safety Assessments:

Analyses of adverse events, physical examination findings, vital signs, and pain on injection utilized the same statistical methods as those used for the primary efficacy assessment.

13. Disposition of Subjects:

Table 1 summarizes patient disposition and reasons for early discontinuation by treatment groups. The one patient lost to follow-up was in the Repronex S.C. group and completed all study procedures except the exit physical examination. This patient was included in all the analyses of efficacy and safety and was only technically classified as a non completion. A total of 115 patients were enrolled and started on down regulation with leuprolide acetate. A total of 108 successfully down regulated.

Table 1
(Sponsor's Table 3)
Disposition of Subjects

Parameter	Repronex™ I.M. N=36	Repronex™ S.C. N=36	Pergonal® I.M. N=36	Enrollment Failure (not randomized) N=7
Enrolled	36	36	36	7
Randomized	36	36	36	0
Completed Study	25	27	21	0
Did not Complete Study	11	9	15	7

Reasons for Discontinuation

Parameter	Repronex™ I.M. N=11	Repronex™ S.C. N=9	Pergonal® I.M. N=15	Enrollment Failure (not randomized) N=7
Failure to Down Regulate	0	0	0	5
Non-Compliance	0	0	0	2
Decline in E2 Levels	0	0	4	0
Inadequate Response	10	7	7	0
Protocol Violation	0	0	1	0
Risk of OHSS	0	1	3	0
Elevated E2 Levels/ Too Many Follicles	1	0	0	0
Lost to Follow-up	0	1	0	0

14. Protocol Violations:

Thirty subjects had minor protocol deviations during the conduct of this study. Most did not affect evaluability of the subject.

15. Demographic Characteristics:

There were no statistically significant differences at baseline between the three treatment groups for age, weight, height, body mass index, or race.

16. Results:

a. Efficacy:

1.) Ovulation:

The primary efficacy variable was ovulation. The number and percentage of subjects who ovulated was calculated, analyzed, and compared across the three treatment groups. The intent-to-treat analysis for all subjects who were randomized and had cycles initiated with exogenous gonadotropins is shown in Table 2. There were no significant differences among the treatment groups.

Table 2
(Sponsor's Table 5)
Primary Efficacy Variable (Ovulation)
Intent-To-Treat

Parameter	Repronex™ I.M. N=36	Repronex™ S.C. N=36	Pergonal® I.M. N=36	p-value
Ovulation (%)	23 (63.9)	25 (69.4)	21 (58.3)	NS

For the subset of subjects who received hCG, there was also no significant differences among the three treatment groups.

2.) Secondary Variables:

Several secondary variables were analyzed on an intent-to treat basis and also for subsets of subjects who received hCG and who ovulated. The intent-to-treat analysis is shown in Table 3.

Table 3
(Sponsor's Table 7)
Secondary Efficacy Variables
Intent-To-Treat

Parameter (%)	Repronex™ I.M. N=36	Repronex™ S.C. N=36	Pergonal® I.M. N=36	p-value
Met hCG criteria	27 (75.0)	30 (83.3)	21 (58.3)	0.020
Received hCG	25 (69.4)	27 (75.0)	21 (58.3)	NS
No. of follicles meeting hCG criteria	144	159	115	____
Mean peak serum E2 levels (SD)	1158.5 (742.3)	1452.6 (1270.6)	1314.4 (1268.2)	NS
Chemical pregnancy	4 (11.1)	11 (30.6)	7 (19.4)	0.042
Clinical pregnancy	4 (11.1)	6 (16.7)	7 (19.4)	NS
Continuing pregnancy	4 (11.1)	6 (16.7)	7 (19.4)	NS

The only significant differnces were for subjects who met hCG criteria and for chemical pregnancy. For the "met hCG" parameter, the Repronex S.C. group had a significantly higher percentage of subjects than the Pergonal I.M. group. The five subjects who met hCG criteria and did not receive hCG (2 in the Repronex I.M. group and 3 in the Repronex S.C. group) had hCG witheld because investigators felt that too many follicles had developed.

The Repronex S.C. group had a significantly higher incidence of chemical pregnancies than the Repronex I.M. group.

There were no ectopic pregnancies in this study.

Among 17 subjects with clinical pregnancies, there

were 10 subjects with multiple pregnancies (59%). Four of these 10 subjects had twins (40%). Six of the 10 subjects had triplets or quadruplets (60%). Seven of the 17 subjects with clinical pregnancies had singlets (41%).

b. Safety:

There were no deaths in this study. No subject dropped out because of an adverse event. Five subjects were discontinued (hCG was not given) because the investigators felt that there were too many developed follicles and there was a theoretical risk of developing OHSS or having a high multiple pregnancy if hCG was given. This was a clinical judgment, however, and not a response to an existing adverse event.
There were three subjects who were hospitalized.

The most serious case was that of a subject with severe OHSS who was hospitalized for 22 days. A second subject was hospitalized overnight because of a pelvic infection and a third subject was hospitalized overnight because of pelvic pain.

Seven cases of OHSS occurred. There were 3 subjects each with OHSS in the Repronex S.C. (8.3%) and Pergonal I.M. (8.3%) groups and 1 subject in the Repronex, I.M. (2.8%) group. These incidences were not significantly different.

This study did not assess routine clinical laboratories because both study drugs are approved and there is a very large clinical database documenting the safety of these drugs.

Pain on injection was uniformly mild for all three treatment groups. During the 12 days of gonadotropin treatment, there were no statistically significant differences in the mean pain scores among the three treatment groups. There were no injection site reactions noted in any treatment group. Overall, Repronex S.C. and I.M. and Pergonal I.M.

injections were well tolerated.

B. STUDY 99-02. A Randomized, Open-label, Parallel Group, Multicenter, Efficacy Study Comparing Repronex S.C., Repronex I.M., and Pergonal I.M. in Female Patients Undergoing In vitro Fertilization.

1. Investigators:

Jack Crain, M.D. Charlotte, NC
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William Kuttek, M.D. Memphis, TN
Joe Massey, M.D. Atlanta, GA,
Wayne Maxon, M.D. Margate, FL
James Mayer, M.D. Tampa, FL
Robert McWilliams, M.D. Houston, TX
John Queenan, Jr., M.D. Mt. Pleasant, SC
William Schoolcraft, M.D. Englewood, CO
Michael Steinkampf, M.D. Birmingham, AL
David Walmer, M.D. Durham, NC
Eric Widra, M.D. Washington, DC
Paul Zarutksie, M.D. Laguna Miguel, CA

2. Objectives of the Study:

The objectives of this study were to determine the therapeutic efficacy and safety of Repronex S.C. compared to Repronex I.M. and Pergonal I.M. in subjects undergoing in-vitro fertilization.

3. Rationale for the Study:

Intramuscular injections of menotropins can be painful and inconvenient to the home-based patient and often requires a partner to administer the medication. Subcutaneous administration of menotropins may provide a more convenient and better-tolerated treatment than intramuscular administration with comparable efficacy.

4. Method of Assignment to Treatment:

Subjects were randomly assigned to receive one of the three

treatments using a randomization code that yielded equal numbers of subjects in each treatment arm.

5. Number of Subjects:

   A total of 189 subjects were enrolled and 186 subjects were randomized.

6. Duration of Clinical Trial:

   One treatment cycle only.

7. Inclusion Criteria:

   a. Signed informed consent prior to screening
   b. Nonsmoking females aged 18-39 years
   c. Regular, ovulatory menstrual cycles
   d. E_2, LH, FSH, PRL, T, DHEA-S, AND TSH levels within normal limits
   e. Hematology, chemistry, and urinalysis within normal limits
   f. Infertility attributable to or in association with either tubal factors, endometriosis, or unexplained causes
   g. Recent semen analysis for male partner
   h. Presence of two normal ovaries
   i. Normal uterus and adnexae by transvaginal ultrasound
   j. No fertility drugs for at least one cycle
   k. No IVF/ART for at least one cycle prior to screening
   l. Normal uterine cavity
   m. Negative serum pregnancy test
   n. Desire to become pregnant

8. Exclusion Criteria:

   a. Any clinically relevant systemic disease

b. Any condition that might interfere with the pharmacokinetics
c. Pregnancy within the past 3 months
d. Body mass index greater than 32
e. More than three previous ART cycles
f. Previous ART failure with a poor response to gonadotropins
g. Abnormal uterine bleeding
h. Active substance abuse
i. History of chemotherapy or radiotherapy
j. Pregnant, breast feeding, or contraindication to pregnancy
k. Inability to comply with the protocol
l. Obvious leukospermia for male partner
m. Intolerance or allergy to any gonadotropin
n. Experimental drug study participation in past 60 days

9. Trial Period:

December 21, 1997-June 22, 1998

10. Dosage and Mode of Administration:

Each subject was down regulated with daily injections of leuprolide acetate (up to 20 days) beginning 7 days before the anticipated onset of menses until serum estradiol concentrations were ≤ 40 pg/mL. Leuprolide acetate was continued until the day before hCG administration.

The starting doses of Repronex and Pergonal were 225 IU/day x 5 days after which patient specific adjustments could be made by the investigator based on ultrasound findings and estradiol concentrations within a range of 150 to 450 IU/ day for a total duration of no more than 12 days.

11. Efficacy Assessments:

The primary efficacy variable was the number of oocytes retrieved per cycle.

Secondary efficacy variables included mature oocytes retrieved, percentage of patients with oocyte retrieval, peak serum E_2 levels, percentage of patients with embryo

transfer, percentage of patients with chemical pregnancy, percentage of patients with clinical pregnancies, and percentage of patients with continuing pregnancies.

12. Safety Assessments:

Adverse events and injection site reactions to pain were evaluated.

13. Disposition of Subjects:

Table 4
(Sponsor's Table 15B)
Disposition of Subjects

Parameter	Repronex IM	Repronex SC	Pergonal IM
Randomized	N=65	N=60	N=61
Reason for Discont.	N (%)	N (%)	N (%)
Inadequate Response	4 (6.2)	4 (6.7)	3 (4.9)
Adverse Event	0	1 (1.7)	0
Risk of OHSS	0	0	1 (1.6)
Protocol Violation	1 (1.5)	0	0
Patient Non-Compliance	0	0	1 (1.6)
Patient Choice	1 (1.5)	0	0
Lost to follow-up	1 (1.5)	1 (1.7)	0
Other	2 (3.1)	4 (6.7)	1 (1.6)
Completed Study	56 (86.2%)	50 (83.3%)	55 (90.2%)

A total of 189 subjects were enrolled in the study and started on down regulation with leuprolide. Three of the subjects were not randomized to gonadotropins because of non-compliance with leuprolide administration or because they failed to achieve adequate down regulation with leuprolide as required in the protocol.

14. Protocol Violations:

Numerous minor protocol violations occurred during the conduct of this clinical trial. Most did not affect the evaluability of the subjects and involved the requirement that hCG be administered when at least 3 follicles reached a diameter of 16mm or greater as measured by transvaginal ultrasound.

Five subjects had two follicles ≥16mm and 1 follicle between 14.9mm and 15.6 mm in diameter. They were analyzed as having met the hCG criteria.

Three subjects inappropriately received hCG before the follicle size criteria were met. They were analyzed as treatment failures.

One subject mistakenly took only 75 IU of Pergonal on days 1 through 4. She was analyzed as a treatment failure.

15. Demographic Characteristics:

There were no statistically significant differences at baseline among the three treatment groups regarding age, weight, height, body mass index, or race.

16. Results:

a. Efficacy:

The primary efficacy variable was the number of oocytes retrieved. In each of the three treatment arms, the mean number of oocytes retrieved per subject was calculated, analyzed, and compared across the treatment groups. Table 5 shows the results of an intent to treat analysis of all subjects who were randomized and had cycles initiated with exogenous gonadotropins. There were no statistically significant or clinically meaningful differences among the three treatment arms.

Table 5
(Sponsor's Table 3)
Primary Efficacy Variable - Intent to Treat

Parameter	Repronex™ I.M.	Repronex™ S.C.	Pergonal® I.M.	P-Values		
				RepIM vs. PergIM	RepSC vs. PergIM	RepIM vs. RepSC
	N=65	N=60	N=61			
Total oocytes retrieved (SD)	13.6 (±7.7)	12.7 (±7.8)	13.6 (±7.8)	0.98	0.50	0.51
Mature oocytes retrieved (SD)	9.4 (±6.1)	8.6 (±6.8)	9.3 (±6.1)	0.90	0.58	0.49

Several secondary efficacy variables were analyzed. Table 6 shows the results of an intent to treat analysis of all subjects who were randomized and had cycles initiated with exogenous gonadotropins. There were no statistically significant differences among the three treatment arms regarding any of the secondary variables analyzed.

Table 6
(Sponsor's Table 5)
Secondary Efficacy Variables - Intent to Treat

Parameter	Repronex™ I.M.	Repronex™ S.C.	Pergonal® I.M.	P-Values		
				RepIM vs. PergIM	RepSC vs. PergIM	RepIM vs. RepSC
	N=65	N=60	N=61			
Pts. With oocytes retrieval (%)	61 (93.8)	55 (91.7)	56 (91.8)	0.66	0.98	0.64
Pts. with embryo transfer (%)	58 (89.2)	51 (85.0)	55 (90.2)	0.86	0.39	0.48
Peak serum estradiol (SD)	2197.4 (1142.5)	2028.9 (1422.8)	2232.2 (1349.7)	0.44	0.21	0.24
Pts. with chemical pregnancy (%)	31 (47.7)	35 (58.3)	32 (52.5)	0.59	0.52	0.23
Pts. with clinical pregnancy (%)	25 (38.5)	30 (50.0)	24 (39.3)	0.92	0.24	0.19
Pts. with continuing pregnancy	24 (36.9)	29 (48.3)	19 (31.1)	0.49	0.53	0.20

There were five ectopic pregnancies, one each in the Repronex I.M. and S.C. treatment arms and three in the Pergonal treatment arm.

Table 7 summarizes the number and type of multiple pregnancies in each treatment group.

Table 7
Multiple Pregnancies

Parameter	Repronex IM	Repronex SC	Pergonal IM
No. Pts. with continuing pregnancy	24	29	19
No. Pts. with Singlets (%)	14 (58.3)	14 (48.3)	5 (26.3)
No. Pts. with multiple pregnancies (%)	10 (41.7)	15 (51.7)	14 (73.7)
No. Pts. with Twins (%)	7 (70.0)	9 (60.0)	10 (71.4)
No. Pts. with Triplets (%)	3 (30.0)	3 (20.0)	3 (21.4)
No. Pts. with Quadruplets (%)	0 (0.0)	3 (20.0)	1 (7.1)

b. Safety:

Table 8 lists the most frequently reported adverse events by treatment arms.

Table 8
(Sponsor's Table 9)
Patients with Most Frequent Adverse Events

Adverse Event	Repronex™ I.M. N=65	Repronex™ S.C. N=60	Pergonal® I.M. N=61
Injection Site Edema (%)	1 (1.5)	8 (13.3)	1 (1.6)
Injection Site reaction (%)	2 (3.1)	8 (13.3)	2 (3.3)
Nausea (%)	4 (6.2)	5 (8.3)	2 (3.3)
Abdominal Cramping (%)	5 (7.7)	2 (3.3)	4 (6.6)
Abdominal Pain (%)	3 (4.6)	4 (6.7)	3 (4.9)
Vaginal Hemorrhage (%)	6 (9.2)	1 (1.7)	3 (4.9)
Ovarian Disease (%)	1 (1.5)	4 (6.7)	2 (3.3)
Headache (%)	3 (4.6)	3 (5.0)	0 (0)
Enlarged Abdominal (%)	3 (4.6)	2 (3.3)	0 (0)
Vomiting (%)	0 (0)	3 (5.0)	0 (0)
OHSS	1 (1.5)	2 (3.3)	2 (3.3)
Ectopic Pregnancy	1 (1.5)	1 (1.7)	3 (4.9)

Two specific adverse events of particular interest

with gonadotropin treatment for IVF are ovarian hyperstimulation syndrome and ectopic pregnancy. There was one incident of OHSS in the Repronex I.M. group, two in the Repronex S.C. group and two in the Pergonal I.M. group. This is an incidence of 1.5% to 3.3%. One of the subjects in the Repronex S.C. group had a mild case of OHSS and the second subject had a moderate case of OHSS. Most of the cases of OHSS in this study occurred after hCG administration and during the initial days of pregnancy. None resulted in premature discontinuation and 4 of the 5 subjects had a continuing clinical pregnancy.

One subject in the Repronex I.M. group, one subject in the Repronex S.C. group, and three subjects in the Pergonal group had ectopic pregnancies.

One specific adverse event occurred in a subject who received Repronex S.C. that should be mentioned. The subject had a temporal lobe seizure that occurred 19 days after the last dose of Repronex during the early days of pregnancy. The subject had no history of seizure diathesis or other neurological abnormalities. The relationship to Repronex in unknown, but appears not to be related to the study drug. The investigator reported this event as a severe adverse event, but not medically serious.

There were 6 serious adverse events that occurred in this study including one that occurred in the Repronex S.C. group. This subject had an ectopic pregnancy. Three other serious ectopic pregnancies occurred in the study and two serious cases of OHSS occurred, both in the Pergonal I.M. group.

The most striking difference in adverse events between treatment arms is the considerably higher incidence of injection site reactions seen in the Repronex S.C. group than in the Repronex I.M. and Pergonal I.M. groups. The only subject in the study to discontinue because of an adverse event was a

subject in the Repronex S.C. group who discontinued because of an injection site reaction.

Pain on injection was assessed by each subject on each day of gonadotropin treatment using a digital scale numbered 1 through 10 with 1 being no symptoms and 10 being severe pain. The mean average pain score for days 1-12 of gonadotropin treatment was 2.7 for the Repronex I.M. and Pergonal I.M. treatment arms and 3.3 for the Repronex S.C. treatment arm. There were 3 days (1,2. and 5) when Repronex S.C. subjects reported statistically significantly higher mean pain scores than Repronex I.M. and Pergonal I.M. The mean pain scores assessed by each subject during the first 5 days of gonadotropin injections are listed in Table 9. Differences between treatment arms lessened after the fifth injection day.

Table 9
Mean Daily Pain on Injection Scores

Injection Day	Repronex I.M.	Repronex S.C.	Pergonal I.M.
1	2.7	3.6	2.7
2	2.9	3.8	2.6
3	2.7	3.3	2.6
4	2.6	3.4	2.9
5	2.5	3.6	2.6

C. Study Meno 96/01 NL. Efficacy and Safety of a New hMG Preparation (Menogon) After Subcutaneous Injection in an In vitro Fertilization Program.

This uncontrolled clinical trial of 100 subjects provides some additional safety data on subcutaneous administration. The drug studied (Menogon) is the menotropins product manufactured and distributed in Europe by Ferring GmbH. It is sourced from the same bulk active drug as Repronex, but has a slightly different formulation with less lactose (5 mg/vial) than Repronex and is manufactured at a different site (Kiel, Germany) than Repronex.

The main objectives of this trial were to study the effect of subcutaneously administered Menogon on FSH levels and to assess local tolerance to Menogon administered subcutaneously for one cycle of IVF treatment.

Active inquiries into adverse events were made and injection sites were inspected for local reactions.

The mean FSH level increased form 5.6 IU/L at the start of stimulation to 19.7 IU/L after 7 days, and decreased slightly to 18.7 IU/L on the day of hCG administration.

Local tolerance was scored after 7 days of stimulation and on the day of hCG administration. After 7 days, moderate and severe erythema was observed by the physician in 23% of the subjects (4 severe cases). On the day of hCG administration, moderate and severe erythema was observed in 21% of the subjects (3 severe cases). After 7 stimulation days, pain was reported in 16% of subjects (5 severe cases) and pruritus reported in 8% of the subjects (1 severe case). None of the subjects postponed or skipped one or more injections because of adverse events.

There were 3 subjects with OHSS of which 2 were serious requiring hospitalization.

IX. Postmarketing Clinical Studies:

No postmarketing clinical trials are required.

X. Safety Update:

A safety update was submitted March 24, 1999. It included the adverse events observed in the two controlled clinical trials and the one uncontrolled clinical trial that are summarized in this NDA review. No new reports are submitted since all three clinical trials are completed and adverse events were submitted in the original submission and the amendment submitted March 24, 1999. No long-term effects of treatment are reported.

XI. Reviewer's Overall Evaluation and Conclusions:

Repronex is already approved under ANDAs 73-598 and 73-599 for induction of ovulation and to stimulate the development of multiple follicles in ovulating patients participating in an in vitro fertilization program (and in men for the stimulation of spermatogenesis) in which intramuscular administration is the approved route of administration. It is equivalent to Pergonal.

This application seeks the approval of a new route of administration based on clinical trials that demonstrate that the subcutaneous administration of Repronex is also safe and effective for the same indications as those already approved for the

intramuscular administration of Repronex.

Pharmacokinetic data are not intended to demonstrate bioequivalence of the subcutaneous and intramuscular routes of administration and did not do so.

The clinical benefits of Repronex and other menotropin drugs are well established. Menotropins have been approved for over 30 years for induction of ovulation and have been approved for several years to induce ovarian follicle development in ovulatory patients participating in ART programs such as IVF, GIFT, AND ZIFT. Menotropins have also been approved for many years to induce spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism.

Studies 97-01 and 97-02 are the pivotal clinical trials providing the efficacy data for this application. Both trials had randomized, parallel groups, multicenter designs comparing Repronex I.M., Repronex S.C., and Pergonal I.M. In study 97-01, oligoovulatory infertile female patients, most of whom had a diagnosis of polycystic ovary disease, were evaluated for induction of ovulation. In study 97-02, female patients undergoing IVF, were evaluated for multiple follicle development.

The response variable used for power calculations for required sample size in study 97-01 was the proportion of subjects who ovulated during treatment. There was 70% power to detect a relative difference of 35% if the ovulation rate was 70% in the reference groups with 38 evaluable subjects in each group. A sample of 38 subjects per group was selected. A total of 115 subjects were enrolled and started down regulation with leuprolide acetate. A total of 108 subjects successfully down regulated and 36 subjects were randomized to each treatment arm. There were no statistically significant differences among the treatment groups. The percentage of subjects ovulating in each group was 69.4% for Repronex S.C., 63.9% for Repronex I.M., and 58.3% for Pergonal I.M.

There were no statistically significant differences between any treatment pair in the proportion of subjects with clinical or continuing pregnancies. The percentage of subjects with clinical and continuing pregnancies in each group was 16.7% for Repronex S.C., 11.1% for Repronex I.M., and 19.4% for Pergonal I.M.

Initial studies conducted by another sponsor many years ago using Pergonal I.M. in subjects with polycystic ovaries who were not down regulated yielded an ovulation rate of 76% and a pregnancy rate of 26%, both of which are higher rates than those found in this study. In the original Pergonal studies, the multiple pregnancy rate in PCO subjects was 17%, all twins. In this study, the multiple pregnancy rate (based on very small numbers) for Repronex S.C. was 50%, for Repronex I.M.-50%, and for Pergonal I.M.-71%.

In the original Pergonal induction of ovulation studies, 75% of all multiple pregnancies were twins and 25% of all multiple pregnancies were three or more concepti. In this study, 66.7% of the three multiple pregnancies in the Repronex S.C. group were quadruplets and 33.3% were twins. In the Repronex I.M. group, 100% of the multiple pregnancies (two) were triplets. In the Pergonal I.M. group, 60% of the multiple pregnancies were twins, 20% were triplets, and 20% were quadruplets. No explanation is known for these findings in this study.

There were no injection site reactions noted in any treatment group. Pain on injection was said to be uniformly mild for all treatment groups.

Adverse events were not significantly different among groups. The incidence of serious adverse events was low in all three treatment arms.

Overall, Repronex S.C. is safe and effective for the induction of ovulation.

In study 97-02, estimates of power for determination of the sample size were based on the assumption that the expected mean of oocytes retrieved per cycle was ten with a standard deviation of two in the reference groups. Power calculations were performed based on a =0.05 (assuming a two-tailed test) and the power=80%. Based on this calculation, there was 80% power to detect a change in the number of oocytes equal to 1.2 (i.e., 10 vs. 8.8) with a sample size of at least 44 subjects per group. This study had a greater than 80% power since a sample size of at least 50 subjects per group was selected and in fact 60 subjects (at least) were randomized into each treatment arm.
There were no statistically significant or clinically meaningful differences among the three treatment arms regarding the primary and secondary efficacy variables.

In the Repronex S.C. group, 48.3% of subjects had continuing pregnancies while 36.9% of subjects in the Repronex I.M. group had continuing pregnancies and 31.1% of subjects in the Pergonal I.M. group had continuing pregnancies.

Multiple pregnancies occurred in 51.7% of Repronex S.C. subjects, 41.7% of Repronex I.M. subjects, and 73.7% of Pergonal I.M. subjects. Of the 15 subjects with multiple pregnancies in the Repronex S.C. group, there were three (20%) with triplets, three (20%) with quadruplets, and nine (60%) with twins. Of the 10 subjects with multiple pregnancies in the Repronex I.M. group there were three (30%) with triplets and seven (70%) with twins. Of the 14 subjects with multiple pregnancies in the Pergonal I.M. group, there were three (21.4%) with triplets, one (7.1%) with quadruplets, and ten (71.4%) with twins. No explanation in given for the high percentage of triplets and quadruplets occurring in this study.

The multiple pregnancy rates found in both study 97-01 and study 97-02 are

greater than those reported for other studies. For example, in Follistim, 31% (84/272) of pregnancies achieved in IVF-ET treatment, were multiple pregnancies. Eight percent (2/24) of the pregnancies conceived in one Follistim study of classical ovulation induction were multiple pregnancies. These rates are also comparable to those found in subjects receiving Metrodin in an ART program (38%, 47/24) and for classical ovulation induction (8%, 1/13).

Administration of Repronex S.C. did result in a higher incidence of injection site reactions compared to Repronex I.M. and Pergonal I.M. These reactions were said to be predominantly mild and self-limited, but did result in one subject discontinuing after 6 days of treatment because of painful, red swelling at the injection site which was reported as being moderately severe.

While the one occurrence of a temporal lobe seizure in a subject 19 days after the last dose of Repronex may not be related to the study drug or to the GnRH agonist (leuprolide acetate), a causal relationship to either drug cannot be ruled out.

Overall, Repronex S.C. is safe and effective when used to stimulate the development of multiple follicles in ovulatory patients participating in an in vitro fertilization program.

XII. Labeling:

Revised draft labeling submitted August 3, 1999 was reviewed, evaluated, and discussed at the labeling meeting of the review team August 6, 1999. Relevant requests for labeling revision will be transmitted to the applicant August 9, 1999. It is expected that the draft labeling will be finalized August 14, 1999.

XIII. Recommendation:

Approval of the application is recommended provided that the labeling is satisfactorily revised.

/S/

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

I concur

/S/ 8/13/99

NDA 21-047
Repronex® (Menotropins for Injection, USP) 75 or 150 IU
Ferring Pharmaceuticals, Inc.

Safety Update Review

The sponsor reported that there are no ongoing trials since this application was submitted. Accordingly, there are no new clinical data to review for this application.

/S/ 8/14/99

I concur

/S/ 8/16/99