CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-663

Medical Review(s)

Menopur™
Medical Officer Team Leader Memorandum

NDA:	**21-663**
Drug:	**Menopur™ (follicle stimulating hormone [FSH] and luteinizing hormone [LH])**
Indication:	**When administered subcutaneously [ ] for the development of multiple follicles and pregnancy in the ovulatory patient participating in an ART program.**
	[ ]
Dosage/Form/Route:	**75 IU lyophilized powder to be reconstituted with 2 ml 0.9% sodium chloride for subcutaneous [ ] injection.**
	[ ]
	[ ]
	For multiple follicular development, the recommended initial dose for patients who have received a gonadotropin-releasing hormone (GnRH) antagonist or GnRH agonist is 225 IU. 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 two days and should not exceed 150 IU per adjustment. The maximum daily dose of Menopur® should not exceed 450 IU and dosing beyond 20 days is not recommended.
Applicant:	**Ferring Pharmaceuticals, Inc 400 Rella Boulevard, Suite 300 Suffern, NY 10901**
Original Submission Date:	**December 29 2003**

Review Completed: **October 29, 2004**
Date of Memorandum: **October 29, 2004**

Background

The first menotropins drug product, Pergonal® received approval in 1970 for the indication of ovulation induction. In 1989, Pergonal received approval for the indication of multiple follicular development in ART. Repronex® was originally approved for the treatment of female infertility under ANDA 73-598/599 for Lederle Laboratories as an equivalent of Pergonal®. On July 03, 1996, Lederle Laboratories transferred ownership of ANDA 73-598 (menotropins) to Ferring Pharmaceuticals, Ind. Repronex® was approved under ANDA 73-598 for induction of ovulation and multiple follicular development in ART when administered by the intramuscular route. The NDA to support the use of Repronex® for the two approved indications when administered by the subcutaneous route (NDA 21-047) was submitted on October 28, 1998 and was approved on August, 27 1999. The NDA submission was based on two controlled, comparative phase III clinical studies:

- 97-01 – for the indication of oligoanovulatory infertile female subjects undergoing ovulation induction therapy
- 97-02 – for the indication of normally cycling female subjects undergoing in vitro fertilization

In March 1998, the sponsor initially proposed a new "more purified" Repronex® [Menopur™] formulation that would reduce injection site reactions. The sponsor was told at the 1998 meeting that an NDA should be submitted for the new purified Repronex® formulation, since this was not a simple CMC change and clinical studies would be required. The first clinical protocols for a clinical IVF study and a bioequivalence study (comparing Repronex® to the purified Repronex® [Menopur™] formulation) were submitted for Menopur™ in 2000. A guidance meeting was held with the sponsor on January 2001 to clarify clinical and chemistry issues related to their supplemental NDA submission for the highly purified Menopur™ formulation. The sponsor was told that a clinical study for each indication would be required for the new NDA, [ ]. In addition, the sponsor was informed by the Division that the formulations used in the clinical studies should be identical to the to-be marketed formulation.

A preNDA meeting was held with the sponsor on March 03, 2003 to discussion chemistry, clinical pharmacology, clinical and other issues for approval of the new Menopur™ formulation. During this meeting the Division noted three major efficacy issues and one issue relative to a superiority claim based on safety. These issues are as follows:

- The Division will consider [ ]

- An analysis including statistical adjustments for baseline co-variants for trial 2000-02 (U.S. In Vitro Fertilization trial) will be considered a secondary analysis. The Division agreed on October 11, 2001 that the stated delta of 3.9 oocytes will be accepted as a clinically meaningful difference in the test of non-inferiority. The analysis presented in

the briefing document shows that the lower bound of the 95% confidence interval (-4.4) does not exclude a difference of -3.9 oocytes. Therefore, non-inferiority of — Repronex® SC to Repronex® SC has not been established in this trial.

- The Division will need information on the formulation of recombinant FSH (Gonal-f®) utilized in the European/Israeli trial for In Vitro Fertilization to determine if this is the same formulation of this drug products approved in the United States. The Division is supportive of a trial that looks at pregnancy as a primary endpoint. If efficacy is demonstrated, data from this trial may be sufficient for this indication with — Repronex® SC. Since the European/Israeli clinical data may be important for clinical safety and efficacy assessments, the Sponsor needs to bridge the formulation used in this trial to the to-be-marketed product via a bioequivalence study.
- Any superiority claims ([ ]) for the HP-Repronex® formulation would require two prospectively designed (to show superiority) clinical trials. Therefore, no safety superiority claims for — -Repronex® will be considered.

NDA 21-663 was received on December 29, 2003, and filed on February 27, 2004.

Chemistry, Manufacturing and Controls (CMC)

The drug substance is manufactured by [ ] The drug substance is — purified from large quantities of urine collected by postmenopausal women (the same starting materials as used for the approved menotropins product, Repronex® [NDA 21-047]). Both FSH and LH are purified [

] [

] The drug substance has a 25-fold lower amount of contaminating urinary proteins compared to Repronex®. The drug substance is stable for 48 months at 2-8°C, the recommended storage temperature.

The drug product is manufactured by Cardinal Health, Albuquerque, NM. It contains 75IU FSH activity and 75 IU LH activity with 20 mg of lactose, 5 mcg of polysorbate 20 and small traces of sodium phosphate (to maintain the pH). The bulk solution is — lyophilized — — The sterile lyophilized preparation is contained in a glass vial with a rubber stopper and metal overseal.

A categorical exclusion was granted for the environmental assessment. The proposed expiration dating period of 24 months at 5°C and 25 °C is acceptable. The cGMP inspection is pending.

Two information request letters were sent to the Sponsor

The first sent on 3/12/04 was a request to provide:

- a clear description of the production of the [ ] and an estimate of the total FSH and LH activity and protein activity contained in [ ] [ ]
- additional — testing to the drug substance specifications
- the test method and proposed acceptance limits for percent protein in the drug product

The second sent 7/27/04 was a request to:

- provide LH bioassay data for [ ]

- provide data regarding the amount of hCG present in Menopur drug substance
- delete the first two sentences of the second paragraph in the Description section of the package insert
- correct the typographical error in the table of proposed specifications for the drug substance for the acceptance limit for LH Bioassay to change FSH IU to LH IU

All requests were adequately addressed. The Chemistry reviewer concludes that the manufacturing processes for both drug substance and drug product are adequately described and the specifications for both are adequate. The drug product stability is adequate to support an expiry date of 24 months at either refrigerated or room temperature.

From a CMC point of view, the NDA is approvable pending an acceptable cGMP inspection.

Microbiology

All reviewed parameters were found to be acceptable. No unresolved deficiencies were noted at the end of the review. The Microbiology reviewer concluded that the information provided in the application is adequate to support approval form a product quality microbiology perspective.

Product Name

The original tradename proposed by the company (Repronex®-[redacted] was discussed at the preNDA meeting held 02-Mar-03. The Chemistry Review Team recommended that an alternate tradename for Repronex®-[redacted] as the initials [redacted] would not be acceptable, and the sponsor should clearly distinguish between the two formulations (Repronex® and Repronex®-[redacted]. The sponsor then chose a new tradename, Menopur® (submitted with the NDA on 29-Dec-03), to replace the original designation of the product, Repronex® [redacted] The initial review of the Division of Medication Errors and Technical Support dated February 10, 2004 found no objections to the use of the proprietary name Menopur®. However a second review dated October 12, 2004 concurred in that decision.

Pre-clinical Pharmacology and Toxicology

The Pre-clinical Pharmacology reviewer concluded that given the long history of human use of FSH and LH drug products from a toxicological standpoint there were no new safety issues associated with the use of Menopur®. Further, there were no unresolved toxicology issues and from a Pharmacology/Toxicology perspective, the NDA can be approved.

Office of Clinical Pharmacology and Biopharmaceutics

The main issue in terms of influence on approvability that the Office of Clinical Pharmacology and Biopharmaceutics (OCPB) was asked to address was the bioequivalence of the formulation of Menopur used in the European/Israel study, 0399E (the study supporting safety and efficacy of the subcutaneously-administered Menopur for multiple follicular development in IVF), to that of the to-be-marketed formulation in the U.S.. Information to assess bioequivalence was provided in Study 2003-02, "A clinical study to assess the bioequivalence of the proposed U.S. commercial formulation of menotropins relative to the currently marketed European formulation of menotropins for injection". This was a multi-center, randomized, open-label, single-dose, two-treatment period, crossover study in healthy female subjects. To induce pituitary down-regulation, subjects received Lupron Depot (3.75 mg IM) 28 days and then 7 days prior to the first treatment period. Fifty-two (52) subjects had completed data from the 2 treatments and only those were used for the final BE analysis. The bioequivalence was based only on serum FSH determinations. The 90% C.I. values of Cmax and AUC were found to be within the Agency recommended limits of 80% -120%.

Because the bioequivalence study was critical to approval of the subcutaneous route of administration for the multiple follicular development in IVF indication, the Division of Scientific Investigations was asked to inspect the site of the bioequivalence study. The DSI investigator wrote that accuracy was not assured for the commercially-available immunoenzymometric assay, [redacted] procedure for FSH in human serum. The reviewer wrote that data was not provided to demonstrate that the [redacted] assay accurately measured FSH concentration in human serum spiked with the reference standard supplied by the Sponsor. Specifically, in the freeze/thaw experiment, the measured concentration of FSH in human serum samples spiked with FSH supplied by the Sponsor was determined to be only 15-50 % of the spiked concentration. The conclusion of the DSI investigator was that Study 2003-02 should **not** be accepted for review until the accuracy of the [redacted] assay is demonstrated for serum samples spiked with Ferring FSH. Furthermore, appropriate freeze/thaw, long term and bench top stability should also be demonstrated.

Ferring was asked to justify the DSI findings. Ferring responded with a facsimile (dated October 21, 2004) in which they stated that the assay standards used with the [ ] (for FSH assay) had a different source than that used for Ferring manufactured FSH and a mean "normalization factor" of 0.537 would have to be used in order to compare the two sources. The sponsor clarified that the normalization factor was not used in the BE study and that the same lot of API FSH was used in both, US and EU formulations of Menopur. This argument was accepted by OCPB in consultation with the Office of New Drug Chemistry. Therefore, the OCPB reviewer accepted Study 2003-02 as evidence of bioequivalence between the European and US formulations.

Based on the above discussion, the Office of Clinical Pharmacology and Biopharmaceutics find that the NDA is acceptable.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

The evaluative report of the clinical inspections for NDA 21-663 summarized inspections at three clinical sites. Two of these sites (Dr. Webster-Baton Rouge,LA. [ ]
were found to be in compliance with U.S. Federal Regulations and good clinical investigational practices. Protocol violations were observed at the investigational site of Dr. Paul Devroey-Brussels Belgium. However it was determined that the violations did not negatively impact the reliability or integrity of the data submitted in the NDA. Overall the conclusion was that the data submitted by Drs. Devroey, Webster [ ] appear to be adequate to support the submission.

Clinical Efficacy and Safety

[redacted]

[ ]

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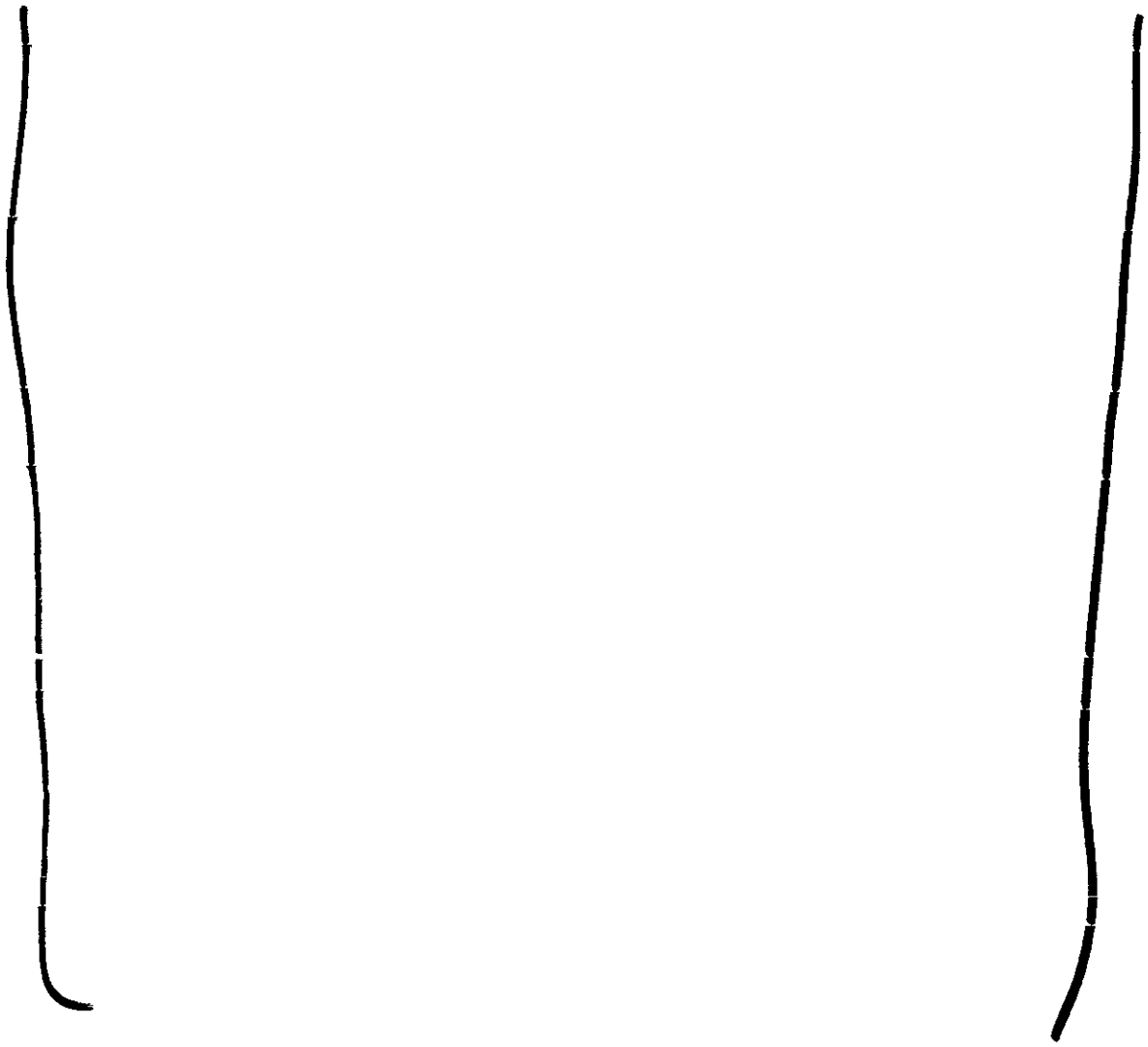

There were no deaths. There were 6 subjects terminated adverse events in Study 2000-01. These were all subjects with Ovarian Hyperstimulation Syndrome (OHSS) or the risk for this problem. There were 1 serious adverse events (severe OHSS) occurring in the subcutaneously-administered Menopur™ treatment arm. The safety profile of Menopur™ demonstrated in Study 2000-01 was acceptable.

Multifollicular Development in IVF

Study 2000-02

Study 2000-02 was a Phase 3, randomized, open-label, multicenter (15) study, with a non-inferiority design, conducted in the U.S. to compare the safety and efficacy of Menopur™

administered by subcutaneous and intramuscular injection to Repronex® administered by subcutaneous injection in subjects who had pituitary desensitization with leuprolide acetate prior to controlled ovarian stimulation as part of an IVF/ET cycle. Subjects were to be enrolled if they were infertile due to tubal factor, endometriosis or unexplained causes. Subjects were to have regular ovulatory menstrual cycles of 24-35 days as well as an objective measure of ovulation, and normal FSH, PRL, DHEAS and TSH levels. Subjects were also required to be nonsmoking, 18 – 39 years of age, and have normal uterus, adnexae and ovaries (both) on ultrasound. A subject whose male partner had associated male factor was accepted only if donor sperm were utilized. A total of 199 subjects were enrolled into the study and started on leuprolide acetate for purposes of down regulation of the pituitary. Following down regulation (defined as estradiol ≤ 45 pg/mL and endometrial thickness of ≤7 mm), 190 subjects were randomized in a 1:1:1 fashion to 225 IU of Menopur™ for subcutaneous or intramuscular administration or 225 IU of Repronex® for subcutaneous administration. The starting dose of 225 IU for all three treatments were maintained for 5 days and then dosing was individualized to a maximum daily dose of 450 IU for a total duration not to exceed 12 days. Treatment was for 1 cycle only.

The primary efficacy variable was the total number of oocytes retrieved per subject. Non-inferiority was to be declared if the lower bound of the 2-sdied 95% confidence interval of the difference in mean number of oocytes retrieved excluded a difference greater than a mean of 3.9 oocytes in favor of the comparator. Secondary efficacy variable assessed included the number of mature oocytes retrieved per subject, the number (and percentage) of subjects with oocyte retrieval, the number (and percentage) of subjects with embryo transfer, and the number and percentage of chemical, clinical and continuing pregnancies. The results for the ITT analysis are shown in Table 2. The Sponsor originally submitted both 1-sided 95% and 2-sided confidence interval testing of the primary efficacy data. The Division maintains that 1-sided 95% confidence interval testing is inappropriate and only the 2-sided 95% confidence intervals are shown in the table.

Table 2 – Study 2000-02
Efficacy Outcome by Treatment Group for IVF, ITT population

	Menopur™ SC N=61	Menopur™ IM N=65	Repronex® N=64
Parameter			
Mean oocytes retrieved per subject-n (SD) Sponsor 2-sided 95% C.I. Division's 2-sided 95% C.I> Division's analysis removing patients who received "Rescue ICSI[c]	13.1 (7.2) (-4.4, 1.7)[a] [-4.5, 1.8][b] [-4.7, 1.7]	13.1 (8.3) (-4.3, 1.7)[a] [-4.3, 1.8][b] [-4.3, 2.1]	14.4 (7.7)
Mature oocytes retrieved per subject-n (SD)[d]	9.9 (4.8)	10.1 (6.4)	10.9 (7.0)
Subjects with oocyte retrieval-n (%)[d]	61 (100)	62 (95.4)	62 (96.9)
Subjects with embryo transfer-n (%)[d]	57 (93.4)[d]	61 (93.8)	62 (96.9)
Subjects with clinical pregnancies[e]-n (%)[d]	18 (29.5)	25 (38.5)	24 (37.5)
Subjects with continuing pregnancies-n (%)[d]	18 (29.5)	25 (38.5)	24 (37.5)
Subjects with live births-n (%)[d]	22 (36%)	36 (55)	30 (47%)

[a] Sponsor submitted using a 2-sided 95% confidence interval for the difference between the Menopur® groups and Repronex® SC
[b]2-sided 95% confidence interval for the difference between Menopur® and Repronex® SC, using Dunnett's adjustment for multiple comparisons.
[c]Subjects who were treated with both IVF and ICSI were removed from the analysis
[d]Secondary analysis – study was not powered to demonstrate statistical significance
[e]Clinical pregnancy was defined as presence of a gestational sac

Neither the Sponsor's analysis nor the Division's analysis supported non-inferiority of subcutaneously-administered or intramuscularly-administered Menopur™ to Repronex®. Secondary efficacy variables numerically are similar. No statistical testing for non-inferiority of Menopur™ to Repronex® on the basis of these secondary efficacy variables was performed.

There were no deaths or dropouts due to adverse events in this study. There were 7 total serious adverse events reported. These include four cases of OHSS (1-Menopur® SC, 2- Menopur® IM and 1 Repronex®), 1 patient with dehydration, 1 patient with a pelvic abscess and 1 patient with a right ovarian rupture. The latter were all in the Repronex®SC group. The safety profile of Menopur™ demonstrated in Study 2000-02 was acceptable.

Study MFK/IVF/0399E

Study MFK/IVF/0399E was an open-label prospective, randomized, multi-center (22), multi-national (Europe and Israel) comparative study that recruited infertile women undergoing assisted reproductive technology procedures [either patients undergoing IVF or patients undergoing IVF

with intra-cytoplasmic injection (IVF/ICSI)]. Study 0399E was conducted outside of the U.S. and the protocol for this study was not sent for FDA regulatory review prior to submission of the study as part of the supportive studies for the NDA. The study was designed to compare the efficacy (evaluate for equivalence) for the endpoint of ongoing pregnancy (fetal heart beat 10 weeks after oocyte retrieval) rate of Menopur™ administered by subcutaneous injection to Gonal-f® administered by subcutaneous injection in subjects who had pituitary desensitization with GnRH agonists prior to controlled ovarian stimulation as part of an IVF/ET cycle. No specific GnRH agonist was prospectively identified and the use of various agonists was allowed during the study. Subjects were to be enrolled if they were infertile and eligible for IVF or IVF plus ICSI. Subjects were to have regular ovulatory menstrual cycles of 24-36 days as well as an objective measure of ovulation and normal FSH, PRL, DHEAS and TSH levels. Subjects were also required to be nonsmoking, less than 18-38 years of age, and have normal uterus, adnexae and ovaries on ultrasound. Subjects whose male partners had male factor were included. A total of 781 subjects were enrolled into the study, randomized and then started on GnRH agonists for purposes of down regulation of the pituitary. Following down regulation (defined as LH < 5 and estradiol ≤ 200 pg/mL and ultrasound confirmation of no ovarian cysts), 727 received either 225 IU of Menopur™ for subcutaneous administration or 225 IU of Gonal-f® for subcutaneous administration. The starting dose of 225 IU for both treatments were maintained for 5 days and then dosing was individualized to a maximum daily dose of 450 IU for a total duration not to exceed 20days. Treatment was for 1 cycle only.

The primary efficacy variable was the ongoing pregnancy rate defined as a fetal heart beat 10 weeks after oocyte retrieval. Non-inferiority was to be declared if the lower bound of the 2-sided 95% confidence interval of the difference in ongoing pregnancy rates between Menopur™ and Gonal-f® excluded a difference greater than 10% in favor of the comparator. Secondary efficacy variable assessed included the number of mature oocytes retrieved per subject, the number (and percentage) of subjects with oocyte retrieval, the number (and percentage) of subjects with embryo transfer, and the number and percentage of chemical, clinical and continuing pregnancies. The results for the ITT analysis are shown in Tables 3 and 4.

Table 3 – Study 0399E
Primary Efficacy Outcome by Treatment Group for IVF, ITT population

Primary Efficacy Parameter	Menopur™ SC	Gonal-f®
Subjects with ongoing pregnancies[a]-		
Sponsor Analysis ITT subjects n (%) 2-sided 95% C.I. of difference[b]	 373 87 (23.3) (-3.3, 8.7)	 354 73 (20.6)
Division's analysis ITT subjects n (%) 2-sided 95% C.I. of difference[c]	 374 90(24) (-2.4, 9.7)	 353 72(20)
Division's analysis – stratified by insemination[d] IVF ITT subjects n (%) 2-sided 95% C.I of difference[c] ICSI ITT subjects n (%) 2-sided 95% C.I of difference[c]	 121 37 (30.5) (-0.3, 22) 240 53 (22.1) (-7.9, 7.4)	 112 22 (19.8) 219 49 (22.4)

[a]Ongoing clinical pregnancy defined by the presence of fetal sac with heart beat 10 weeks after oocyte retrieval

[b] Sponsor's analysis using a 2-sided 95% confidence interval for the difference between the Menopur® groups and Repronex® SC

[c]2-sided 95% confidence interval for the difference between Menopur® and Repronex® SC, using Dunnett's adjustment for multiple comparisons.

[d]Modified ITT stratified at randomization for the type of insemination procedure either IVF or IVF plus ICSI

The analyses of the ITT data as presented by both the Sponsor and the Division support non-inferiority of Menopur™ (European formulation) to Gonal-f®.

Table 4 – Study 0399E
Secondary Efficacy Outcome by Treatment Group for IVF, ITT population

Secondary Efficacy Paramters	Menopur™ SC	Gonal-f®
Mean oocytes retrieved per subject-n (SD)	12.4 (7.5)	13.4 (8.8)
Mature oocytes retrieved per subject-n (SD)	7.4 (5.4)	7.9 (5.6)
Subjects with oocyte retrieval-n (%)	361 (96.8)	339 (95.8)
Subjects with embryo transfer-n (%)	336 (90.0)	315 (89.0)
Subjects with clinical pregnancies[a]-n (%)	98 (26.3)	78 (22.0)

[a]Clinical pregnancy was defined as presence of a gestational sac

The percentage of clinical pregnancies were similar in the subcutaneously- administered Menopur™ treatment arm compared to the Gonal-f® treatment arm. Live birth rates were not determined in this study. There was a higher multiple gestation rate in the Gonal-f® treatment arm (3.1%) compared to the subcutaneously-administered (1.9) Menopur™ treatment arms. No statistical testing for non-inferiority of Menopur™ to Repronex® on the basis of these secondary efficacy variables was performed.

There were no deaths. Seventeen (17) subjects were cancelled for adverse events (10 in the Menopur™ and 7 in the Gonal-f® group). Fifteen (15) of these cancellations were for the risk of OHHS (9 Menopur and 6 Gonal-f). Thirty-two subjects (4.4%) had serious adverse events. Eighteen (18) of these were in the Menopur™ treatment arm and included: 6 ectopic pregnancies, 5 ovarian hyperstimulation syndrome [OHSS] (including one patient that developed a deep vein thrombosis after the diagnosis of OHSS), 3 missed abortions, 2 threatened abortions, 1 gastritis, 1 patient hospitalized with abdominal pain and vaginal bleeding 2 weeks post-transfer and 1 hyperemesis gravidarum. Serious adverse events in the r-hFSH treatment arm included: 4 ovarian hyperstimulation syndrome, 2 ectopic pregnancies, 3 miscarriages, 2 missed abortions, 1 patient hospitalized with abdominal pain 2 weeks post-transfer, and 1 patient with anaphylaxis. The safety profile of Menopur™ demonstrated in Study MFK/IVF/0399E was acceptable.

Discussion and Conclusions

This reviewer agrees with the primary reviewer that Study MFK/IVF/0399E establishes the safety and efficacy of subcutaneously administered Menopur™ (European approved formulation) for multiple follicular development (controlled ovarian stimulation) and pregnancy in an IVF cycle. However, the formulation of Menopur™ utilized in this study is not the formulation sought for marketing in the U.S. A bioequivalence study was performed to link the clinical trial formulation for Study MFK/IVF/0399E to the to-be-marketed formulation in the U.S. The review of the trial appeared to indicate that bioequivalence had been established. However, DSI inspection of the sites for the bioequivalence trial, 2003-02, recommended that this data not be accepted because of assay quality control issues. DSI concluded that data was not provided to demonstrate that the [redacted] assay accurately measured FSH concentration in human serum spiked with the reference standard supplied by the Sponsor. DSI further concluded that Study 2003-02 not be

accepted for review until the accuracy of the [ ] assay is demonstrated for serum samples spiked with Ferring FSH. The OCPB has decided that Ferring's explanation (see above)of these findings is acceptable and, therefore, the bioequivalence trial is acceptable to demonstrate bioequivalence of the to-be-marketed formulation to the clinical trial formulation. This reviewer still has some questions regarding DSI's conclusions. The questions persist despite Ferring's explanation and OCPB acceptance of it. I would recommend that the Division seek the advice of an outside expert [brought in as a Special Government Employee (SGE)] with expertise in clinical chemistry and quality control to review the DSI findings, as well as Ferring's explanation to make a determination as to whether the [ ] assay accurately measured FSH concentration in human serum spiked with Ferring's FSH and ultimately the acceptability of the bioequivalence study. In the meantime, the Division Director must make his determination based on the information at hand. I recommend approval of the subcutaneous route of administration for Menopur™ for IVF, if the Division Director determines that the bioequivalence study is acceptable.

I concur with the primary reviewer that Study 2000-02 failed to demonstrate efficacy for intramuscularly administered Menopur™ for the indication of multiple follicular development and pregnancy in an IVF cycle. It is my recommendation that approval for this route of administration for this indication not be granted. [

] I recommend that approval not be granted for either route of administration of Menopur™ for this indication. .

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

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

/s/

Shelley Slaughter
10/29/04 04:13:07 PM
MEDICAL OFFICER

Daniel A. Shames
10/29/04 04:27:47 PM
MEDICAL OFFICER
I accept Bioequivalence study as valid

Menopur®

NDA 21-663

Date NDA Submitted: December 29, 2003
Review Completed: October 29, 2004

Medical Officer's Review
(Original Review)

Sponsor:	Ferring Pharmaceuticals, Inc. 400 Rella Boulevard, Suite 300 Suffern, NY 10901
Drug name:	
Generic:	Menotropins for injection, USP
Trade:	Menopur®
Chemical:	Human menopausal gonadotropins (follicle stimulating hormone [FSH] and luteinizing hormone [LH])
Pharmacologic category:	Infertility
Proposed Dosage:	Assisted Reproductive Technology (ART): The recommended initial dose for patients who have received a gonadotropin-releasing hormone (GnRH) antagonist or GnRH agonist is 225 IU. 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 two days and should not exceed 150 IU per adjustment. The maximum daily dose of Menopur® should not exceed 450 IU and dosing beyond 20 days is not recommended.
Strength:	Each vial contains 75 IU of FSH and 75 IU of LH activity.
Administration:	Menopur® is supplied in sterile vials as a lyophilized, white to off-white powder or pellet. The patient will dissolve the contents of one to six vials of Menopur® in one to two milliliters of sterile saline and administer subcutaneously or intramuscularly.
Active ingredients:	Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

Proposed indications: Multifollicular development and pregnancy in ART: Menopur® administered subcutaneously or intramuscularly is indicated for the development of multiple follicles and pregnancy in the ovulatory patient participating in an ART program.

[redacted]

Related Submissions:

ANDA 73-598 (original approved urinary menotropin application for Repronex® for induction of ovulation and development of multiple follicles administered intramuscularly)
IND 53,954 (current approved Repronex® formulation)
NDA 21-047 (current approved Repronex® product)
NDA 21-289 (approved Bravelle® product for ovulation induction)

Related documents for the current Repronex® product:

- ANDA 73-598 transferred from Lederle Laboratories 03-Jul-96
- Original NDA submission for Repronex® (NDA 21-047) was submitted 28-Oct-98
- Original Medical Officer's review of the current approved Repronex® product (NDA 21-047) was completed 13-Aug-99.
- Annual Report for Repronex® (NDA 21-047 Serial No. Y-004) submitted 03-Mar-04

Related documents for the Menopur® formulation:

- First discussion of proposed plan to submit an application for a new purified Repronex® formulation (now Menopur®) was contained in meeting minutes dated 10-Mar-98 (Discussed during guidance meeting with Sponsor for IND 53,954 for submission of new application to administer Repronex® via subcutaneous route)
- Protocol for study 2000-02 (IVF) submitted to IND 53,954 submitted to IND 53,954 (Serial No. 007) received 02-Oct-00.
- Revised protocol for study 2000-02 (Modification #1) submitted to IND 53,943 (Serial No. 011) received 20-Feb-01.
- Letter to the Sponsor from the Division dated 12-Oct-01 concerning the clinically meaningful difference proposed for study 2000-02.

- Bioequivalence protocol (2000-03) submitted to IND 53,943 (Serial No. 008) on 20-Oct-00 (to compare approved Repronex® to new purified Menopur® product).
- Teleconference to discuss bioequivalence of the new formulation of Repronex® on 25-Jan-01.
- Protocol for study 2000-01 — submitted to IND 53,954 (Serial No. 012) on 06-Apr-01.
- Pre-NDA meeting on 03-Mar-03.
- Bioequivalence protocol (requested by the Division at Guidance meeting on 03-Mar-03 to bridge overseas formulation used in study MFK/IVF/0399E with formulation used in the two US studies) for study 2003-02 submitted to IND 53,954 on 17-Apr-03 (Serial No. 018).

Related documents for the (Menopur®) formulation:

- Advice letter sent 24-July-03, Revised bioequivalence protocol for study 2003-02 (Serial No. #20) dated 22-Aug-03.
- Second Advice Letter for study 2003-02 sent 28-Oct-03.
- Teleconference between Division Director and Sponsor concerning bioequivalence study 2003-02 (dated 24-Nov-03).
- Pre-NDA meeting held 03-Mar-03, NDA submission received 29-Dec-03.

Table of Contents

Clinical Review for NDA 21-663

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, I recommend approval of the application for Menopur® given subcutaneously for the indication of multiple follicular development and pregnancy in ovulatory patients participating in an ART program. The decision for the Approvable recommendation is based on the data in study MFK/IVF/0399E that was submitted that demonstrated non-inferiority of subcutaneously-administered Menopur® to subcutaneously-administered Gonal-f® in the rate of ongoing (≥10 weeks) clinical pregnancy. The European formulation used in this study was determined to be bioequivalent to the formulation to be marketed in the United States.

A single in vitro fertilization (IVF) study 2000-02 was performed in the United States. The data in Study 2000-02 failed to demonstrate non-inferiority of the intramuscularly-administered Menopur® to subcutaneously-administered Repronex® for the surrogate endpoint of number of oocytes retrieved in an In vitro Fertilization (IVF) program. I recommend that approval not be given for intramuscularly-administered Menopur® for the indication of multiple follicular development and pregnancy in ovulatory patients participating in an ART program

[redacted]

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

[redacted]

In addition, if the Sponsor wants the labeling of Menopur® to reflect use with [redacted] additional clinical studies will need to be performed. The Sponsor should continue to submit post-marketing experience obtained from all countries where the new formulation of the drug is marketed.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Menopur® is a —— purified preparation of the human gonadotropins extracted from the urine of postmenopausal women. It contains equal amounts of follicle stimulating hormone (FSH) and luteinizing hormone (LH).
Menopur® (purified urinary human FSH [u-hFSH]) is a new purified formulation of a currently approved human menotropin product, Repronex®. Repronex® was originally approved for the treatment of female infertility under ANDA 73-598/599 for Lederle Laboratories as an equivalent of Pergonal®.
On 03-Jul-96, Lederle Laboratories transferred ownership of ANDA 73-598 (menotropins) to Ferring Pharmaceuticals, Ind. Repronex® was approved under ANDA 73-598 for induction of ovulation and multiple follicular development in ART when administered by the intramuscular route. IND 53,954 was opened 14-Aug-97 to support Repronex® for the clinical indications already approved, but when administered by the subcutaneous route.

The NDA to support the use of Repronex® for the two approved indications when administered by the subcutaneous route (NDA 21-047) was submitted on 28-Oct-98 and was approved on 27-Aug-99. The NDA submission was based on two controlled, comparative phase III clinical studies:

- 97-01 – for the indication of oligoanovulatory infertile female subjects undergoing ovulation induction therapy
- 97-02 – for the indication of normally cycling female subjects undergoing in vitro fertilization

In March 1998, the Sponsor initially proposed a new "more purified" Repronex® [Menopur®] formulation that would reduce injection site reactions. The Sponsor was told at the 1998 meeting that "an NDA should be submitted for the new purified Repronex® formulation, since this was not a simple CMC change and clinical studies will be required".

The Sponsor the first clinical Protocols for a clinical IVF study and a bioequivalence study (comparing Repronex® to the purified Repronex® [Menopur®] formulation) were submitted for Menopur® in 2000. A guidance meeting was held with the Sponsor on January 2001 to clarify clinical and chemistry issues related to their supplemental NDA submission for the highly purified Menopur® formulation. The Sponsor was told that a clinical study for each indication would be required for the new NDA, [redacted] In addition, the Sponsor was informed by the Division that the formulations used in the clinical studies should be identical to the to-be marketed formulation.

A preNDA meeting was held with the Sponsor on March 2003 to discussion chemistry, clinical pharmacology, clinical and other issues for approval of the new Menopur® formulation. The Sponsor was advised that:

1. Any superiority claims [ ] for the new Menopur® formulation would require additional clinical studies.
2. The Division had concerns that the initial U.S. IVF study results presented by the Sponsor did not demonstrate clinical non-inferiority of the subcutaneous Menopur® product to the approved Repronex® product. The Sponsor proposed submission of a European study (MFK/IVF/0399E) to provide additional support for the ART indication.
3. The Division told the Sponsor to provide 2-sided 95% confidence intervals for the clinical studies. In addition, the Sponsor was told that non-inferiority of Menopur® (administered either subcutaneously or intramuscularly should be based on a non-inferiority limit of 21%.

Reviewer's comment: However, this European study used a different purified Menopur® formulation than the formulation used in the two U.S. studies (2000-01 and 2000-02). The Division stated that since this European study would be critical for the clinical safety/efficacy assessment of the new Menopur® formulation administered subcutaneously, and a bridging study would need to be performed to compare the European formulation to the U.S. formulation. The Sponsor stated that the Menopur® formulation used in the United States is the intended-for-market product.

B. Efficacy

The Sponsor submitted three phase III clinical studies (2000-01, 2000-02 and MFK/IVF/0399E) to support non-inferiority of the purified Menopur® formulation by comparison to an approved gonadotropin product in each clinical study. Studies 2000-02 and MFK/IVF/0399E were submitted to support the first proposed indication of multiple follicular development and pregnancy in ovulatory patients participating in an ART program. [

]

The Division's statistical analysis of the results for Study MFK/IVF/0399E demonstrated non-inferiority of subcutaneously-administered Menopur® to subcutaneously-administered follitropin alfa in the rate of ongoing (≥10 weeks) clinical pregnancy. However, the Division's analysis of Study 2000-02 failed to demonstrate non-inferiority of either the subcutaneously- or intramuscularly-administered Menopur® to subcutaneously-administered Repronex® for the surrogate endpoint of number of oocytes retrieved in an IVF program.

The Division's analysis [redacted]

]

C. Safety

The safety profile for the new Menopur® formulation was obtained from the three submitted clinical studies (2000-01, 2000-02 and MFK/IVF/0399E).

Safety data was drawn from 499 patients undergoing Assisted Reproductive Technology procedures and 120 patients undergoing ovulation induction. In the three clinical studies, the safety of Menopur® was assessed using physical examination, ultrasound evaluation, laboratory testing, and adverse event monitoring.

One hundred twenty-six of the 499 patients (25%) of patients treated with an Assisted Reproductive Technology procedure were enrolled in the United States study (2000-02). It is difficult to compare safety data obtained from Assisted Reproductive Technology performed in Europe (MFK/IVF/0399E) to that of the United States (2000-02) for several reasons. The reasons include: different gonadotropin hormone-releasing agonist use, different criteria for the diagnosis of ovarian hyperstimulation syndrome, and restrictions in some countries of the maximum number of embryos that can be transferred (lowering the multiple pregnancy rates). In addition, the United States study (2000-02) used a urinary menotropin comparator (Repronex®) in contrast to the European study (MFK/IVF/0399E) that used a recombinant follicle stimulating hormone product (follitropin alfa). For these reasons, these two Assisted Reproductive Technology studies were examined separately for safety and not summarized.

All of 120 patients enrolled and treated in the ovulation induction study were recruited in the United States (Study 2000-01). The rate of adverse events, serious adverse events, ovarian hyperstimulation syndrome, and multiple pregnancy rates in this ovulation induction study did not appear clinically different between the Menopur® treated groups when compared to the group treated with the approved Repronex® product. The Sponsor's submitted safety data for [redacted] of ovulation induction and treatment of patients undergoing Assisted Reproductive Technology procedures appears to demonstrate that the safety profile for the new Menopur® formulation was similar to both the currently marketed Repronex® formulation and to a recombinant follicle stimulating hormone product (follitropin alfa).

D. Dosing

Dose recommendations and adjustments for the purified menotropin formulation of Menopur® (purified u-hFSH) are comparable to the dosage and administration instructions in the currently approved label for Repronex® (u-FSH). However, several differences are noted:

2. **Dosage and Administration recommendations for Assisted Reproductive Technology (ART) therapy:**

The initial dose of Menopur® for patients who have received a GnRH antagonist or agonist for pituitary suppression is 225 IU. 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 every two days and should not exceed 150 IU per adjustment. The maximum daily dose of Menopur® should not exceed 450 IU and dosing beyond 20 days is not recommended.

Reviewer's comment: The dosage regimen for multiple follicular development and pregnancy in ovulatory patients participating in an ART program in the proposed label for Menopur® is different than the current labeling for the approved Repronex® product. The current Repronex® product recommends that dosing beyond 12 days (as opposed to – in the new Menopur® label) is not recommended. The maximum duration of therapy in US IVF study (2000-02), was also 12 days.

However, the proposed dose regimen in the proposed label for Menopur® is identical to the dosage regimen for in vitro fertilization study MFK/IVF/0399E. The maximum total duration of therapy for study MFK/IVF/0399E was 20 days, and this study had a large patient population (727 subjects in the Intent-to-Treat Analysis). It would have been optimal for the Sponsor to have similar duration of dosing in both U.S. and European ART studies.

E. Special Populations

This purified human menopausal gonadotropin (Menopur®) is seeking approved for conditions that occur in infertile women. The studied indications for gonadotropin treatment for the new Menopur® formulation are for controlled ovarian hyperstimulation [ ] These indications do not apply to pediatric or geriatric populations. This drug is contraindicated in pregnancy.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Name: Menotropins for injection, USP
Proposed Trade Name: Menopur®
Drug Class: Infertility
Sponsor's Proposed Indications: Multifollicular development and pregnancy in ART: Menopur® administered subcutaneously or intramuscularly is indicated for the development of multiple follicles and pregnancy in the ovulatory patient participating in an ART program.

[ ]

Dosage/Form/Strength: Each vial contains 75 IU of FSH and 75 IU of LH activity.
Administration: Menopur® is supplied in sterile vials as a lyophilized powder. The patient will dissolve the contents of one to four vials of Menopur® in one milliliter of sterile saline and administer subcutaneously or intramuscularly.

Route of Administration: Subcutaneously or intramuscularly

B. State of Armamentarium for Indication(s)

There are two approved gonadotropin products available on the market in the United States for treatment of infertility that contain urinary-derived human follicle stimulating (FSH) and luteinizing hormone (LH) in equal amounts. These FSH/LH preparations are used for multiple follicular development in patients undergoing Assisted Reproductive Technology (ART) therapy and patients undergoing ovulation induction. In addition, several recombinant and urinary-derived human follicle stimulating hormone (FSH) products are also available for the same indications of ovulation induction and multiple follicular development in a patient undergoing ART therapy.

C. Important Milestones in Product Development

The new formulation of Menopur® (menotropins for injection USP) contains the same active urinary-derived h-FSH (and h-LH) as the approved Repronex® formulation; however, the urine from postmenopausal women will be processed using a different purification method. Menopur® was developed by the Sponsor to "remove additional uncharacterized proteins, and therefore, have greater specific activity as measured by biological activity per unit of protein". A vial of highly purified menotropins has a specific activity 30-fold higher than native gonadotropins. The new Menopur® formulation will be available as a freeze-dried cake that is administered and reconstituted in an identical manner to the currently approved Repronex® product.

D. Other Relevant Information

Ferring has marketed menotropins in Europe and the Middle East under the brand name of Menogon® since June 1993. Ferring's approved product Repronex® is only marketed in the United States. The urine from postmenopausal women that is used in all of Ferring's menotropin products is obtained from [ ] The urine collected is used to produce Menopur®, Menogon® and Repronex®. The production process for Menopur® is somewhat similar to Repronex®, although the purification, sterile [ ] and lyophilization process include slightly different steps. The drug product for Menopur® also contains polysorbate 20 and sodium phosphate dibasic to control the pH as compared to sodium phosphate tribasic.

E. Important Issues with Pharmacologically Related Agents

The therapeutic properties and use of human gonadotropins in women has been well documented in the published literature. The clinical data from the approved Repronex® product (NDA 21-047) demonstrated that selected clinically relevant endpoints were similar in efficacy and safety to a urinary gonadotropin reference product. The ~ treatment modalities (ART [ ], produce multiple key clinical variables that can be evaluated including fertilization rate, ovulation rate and ongoing pregnancy rate.

The most significant hazard of gonadotropin therapy is ovarian hyperstimulation syndrome. For Menopur®, it is expected that an overall rate for significant ovarian hyperstimulation syndrome should be similar to that found with other gonadotropin products.

The range of ovarian hyperstimulation syndrome for patients using gonadotropins in the literature was reported as being up to 5%, with a severe ovarian hyperstimulation rates from 0.1–2% for patients using assisted reproductive technology[1,2].

A second, although less common serious adverse event observed with gonadotropin therapy is thromboembolism. Thromboembolism may present with or without ovarian hyperstimulation, and is usually seen in less than 1% of patients with moderate and severe ovarian hyperstimulation. The mechanism for development of thromboembolism may occur in the presence of high serum estradiol levels pre-and post-gonadotropin treatment. The most current worldwide experience with the current approved Repronex® formulation does not document any thromboembolic events.

A third concern is the risk of multiple pregnancies, as there is a known increased risk for both mother and fetuses. [redacted] (2000-01), the rate of multiple pregnancies appears to be approximately equivalent between the Menopur® groups (2 pregnancies in the Menopur® SC group and 4 pregnancies in the Menopur® IM group. In addition, the multiple pregnancies in these groups was lower than that seen in the approved Repronex® group (6 pregnancies) Although this study was not powered to look at a difference in multiple pregnancy rates, no obvious trend of an increased multiple pregnancy rate with use of Menopur® either subcutaneously or intramuscularly is noted.

In the Assisted Reproductive studies, the multiple pregnancy rates seen in the US study (2000-02), the multiple pregnancy rate between the Menopur® groups and the Repronex® group appears to be similar (10 multiple pregnancies in the Menopur® SC group, 13 in the Menopur® IM group and 9 in the approved Repronex® group). In the European study (MFK/IVF/0399E), the rates of multiple pregnancies were almost identical (30 multiple pregnancies in the Menopur® group (8%) compared to 28 in the follitropin alfa group [8%]).

Reviewer's comment: In the opinion of this reviewer, the safety data for Menopur® in terms of serious adverse events, ovarian hyperstimulation syndrome and multiple pregnancies appears to demonstrate a similar safety profile to other approved gonadotropin formulations.

F. Foreign Approvals of new Menopur® formulation:

Menopur® has been marketed overseas since 1999 using a slightly different formulation from the one proposed for use in the United States. There is no indication that the overseas Menopur® formulation has been withdrawn from the overseas market for any reason. The Sponsor has not reported any actions for safety reasons that were initiated by any regulatory authority or by the Sponsor on the currently approved Repronex® formulation or the overseas Menogon® or Menopur® formulations to date.

G. Other Pharmacologically Related Agents Under Study:

None.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please refer to the pharmacologist's, chemist's and microbiologist's reviews for the pertinent findings. No additional pending approvability issues for CMC, Toxicology, Biopharmaceutics, or Microbiology issues are noted for the new Menopur® formulation.

The original tradename proposed by the company (Repronex®- — was discussed at the preNDA meeting held 02-Mar-03. The Chemistry Review Team recommended that an alternate tradename for Repronex® —' as the initials — would not be acceptable, and the Sponsor should clearly distinguish between the two formulations (Repronex® and Repronex® —). The Sponsor then chose a new tradename, Menopur® (submitted with the NDA on 29-Dec-03), to replace the original designation of the product, Repronex® — In an Email dated 06-Oct-04, DDMAC raised an objection to the tradename Menopur® as the product contained detectable amounts of human chorionic gonadotropin (hCG) present in this urinary menotropin product. DDMAC specifically stated in the consult "if the Review Division finds there is no detriment or advantage to the detectable amounts of hCG in these products that can potentially be used promotionally, then DDMAC has no objection." The addition of human chorionic gonadotropin is considered an acceptable component of menotropins.

Reviewer's comment: On this basis, the medical reviewer finds the tradename Menopur® acceptable.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics/Pharmacodynamics

The currently approved formulation of Menopur® has similar chemical and biological properties to native human follicle stimulating hormone (hFSH) and luteinizing hormone (LH).

The Sponsor submitted the protocol for a bioequivalence study (Study 2000-03) comparing the proposed Menopur® formulation (administered subcutaneously and intramuscularly) to the currently approved Repronex® formulation (administered subcutaneously and intramuscularly) to IND 53,943 on 20-Oct-00 (Serial No. 008). The Office of Clinical Pharmacology and Biopharmaceutics reviewed the protocol for the bioequivalence study (2000-03) and made several comments regarding the regulatory bioequivalence criteria (Biopharmaceutics reviewer's comment sent January 23, 2001). The final data for the Menopur® bioequivalence study (2000-03) was submitted with the NDA for Menopur® on 29-Dec-03.

The preliminary conclusion of the Biopharmaceutical reviewer for Study 2000-03 was that the pK analysis demonstrates that the two products (the current Repronex® formulation and the Menopur® formulation) were bioequivalent.

At the preNDA meeting held 03-Mar-03: Study 2000-02 was proposed to support the IVF indication. However, the Sponsor and the Division realized that the results of this study failed to support efficacy of subcutaneously-administered Menopur® for this indication. The Sponsor then discussed submission of an additional IVF study performed in Europe and Israel (MFK/IVF/0399E). The results of the European IVF study (MFK/IVF/0399E) were therefore critical for the clinical safety/efficacy assessment of the new Menopur® formulation subcutaneously. The European IVF study was performed using a different Menopur® formulation with more polysorbate-20 (tween) than the one used in the two United States studies. Therefore, the Division recommended an addition pK study to bridge the European Menopur® formulation with the Menopur® formulation that used in the United States studies (2000-01 and 2000-02). The Sponsor stated that the Menopur® formulation used in the United States is the intended-for-market product and the United States formulation used in studies 2000-01 and 2000-02.

The Sponsor submitted the protocol for the additional requested bioequivalence study 2003-03 to comparing the European and US Menopur® formulations to IND 53,954 (Serial #018) on 22-Jul-03. A bioequivalence protocol amendment (#1) to the bioequivalence study (2003-02) was submitted on 22-Aug-03. A second subsequent advice letter was sent on the bioequivalence study amendment on 28-Oct-03. A teleconference to clarify the Division's advice letter was held on 24-Nov-03. This second bioequivalence study (2003-02) was submitted with NDA 21-663 on 29-Dec-03. The conclusion of the Biopharmaceutical reviewer is that the two Menopur® formulations (the European formulation and the United States formulation) were bioequivalent.

IV. Description of Clinical Data and Sources

A. Overall Data

Previous clinical information:

Two comparative clinical trials (97-01 and 97-02) were originally submitted to demonstrate efficacy and safety for the current approved formulation of Repronex® (See NDA 21-047).

These two clinical trials for approved Repronex® (one study for multiple follicular development in patients undergoing in vitro fertilization and one study for patients undergoing ovulation induction therapy) were reviewed in detail (see previous Medical Officer's Review of 07-Aug-99).

Since 1999, the efficacy and safety data for the current approved Repronex® formulation has been updated in annual reports. Previous clinical information was obtained from the IND for the approved Repronex® formulation (See IND 53,954) and from the NDA for the approved Repronex® formulation (See NDA 21-047). The original clinical data and updates are incorporated into this review by cross-reference.

Current clinical information:

Three controlled clinical studies were conducted to evaluate the efficacy and safety of the new Menopur® formulation.

1. Study MFK/IVF/0399E was a multi-center, multinational, active-controlled, randomized, open-label study for patients undergoing assisted reproductive technology (ART) treatment. Patients in study MFK/IVF/0399E could have a maximum of one treatment cycle with in vitro fertilization or in vitro fertilization with intracytoplasmic injection (ICSI). A total of 727 patients in study MFK/IVF/0399E were treated with at least one dose of gonadotropin therapy. Patients received down-regulation with a gonadotropin-releasing hormone agonist and were treated with either Menopur® or recombinant follicle stimulating hormone (follitropin alfa). The primary efficacy parameter was ongoing pregnancy after one treatment cycle.

2. Study 2000-02 was a randomized, active-controlled, parallel-group, open-label study for patients undergoing assisted reproductive technology (ART) treatment. Patients in 2000-02 could have a maximum of one treatment cycle with in vitro fertilization only. A total of 190 patients in study 2000-02 were treated with at least one dose of gonadotropin therapy. Patients were treated with either Menopur® (intramuscularly) or Menopur® (subcutaneously) or the approved Repronex® (subcutaneously). The primary efficacy parameter was number of oocytes retrieved per cycle.

3. [redacted]

Studies 2000-01 and 2000-02 compared Menopur® administered either intramuscularly or subcutaneously to the approved gonadotropin formulation (Repronex®) administered subcutaneously to determine non-inferiority. Study MFK/IVF/0399E compared Menopur® administered subcutaneously to an approved recombinant human FSH (follitropin alfa) administered subcutaneously.

B. Tables Listing the Clinical Trials

The tables listing the original clinical trials for the currently approved Repronex® formulation were obtained from the Medical Officer's review of NDA 21-047 (dated 13-Aug-99). The data and tables from the currently approved Repronex® formulation were incorporated from the original review by cross-reference. Additional tables listing the three submitted clinical studies, studies 2000-01, 2000-02 and MFK/IVF/0399E, to demonstrate the non-inferiority of the new purified Menopur® (u-hFSH) formulation to the currently approved Repronex® formulation are contained in NDA 21-663 (submitted 29-Dec-03).

Tables from the three submitted clinical studies (studies 2000-01, 2000-02 and MFK/IVF/0399E) for the new purified Menopur® formulation were also incorporated into this review by cross-reference. Additional brief summaries of two previous clinical trials for the currently approved Repronex® formulation are summarized in Appendix 1 - A. Overview of Completed Clinical Trials for NDA 21-047.

C. Post-marketing Experience

Post-marketing experience for the new purified Menopur® formulation was not submitted with NDA 21-663 or in the electronic submission for the three clinical studies (2000-01, 2000-02 and MFK/IVF/0399E). The most current periodic Annual Report for the currently approved Repronex® formulation was submitted to for the time period from August 2002 through August 2003 (See NDA 21-047 Serial No 004-Y). In this current Annual Report, the Sponsor stated that the currently approved Repronex® formulation has not been withdrawn or suspended for any reason during the past year. No deaths were reported in this current Annual Report. Three serious adverse events were noted in the submission including one injection site reaction, one febrile episode after Repronex® injection and one possible allergic reaction to Repronex®.

The Sponsor states that Menopur® (purified menotropin product) has been approved and marketed in 26 countries since approximately 1999.

The formulation approved in these countries is identical to the formulation used in study MFK/IVF/0399E and the major difference from the proposed to-be-marketed U.S. formulation only is the amount of polysorbate 20. These countries include the Belgium, France, Germany, Switzerland, Ireland, Israel and the United Kingdom.

D. Literature Review

Published literature articles referred to in this review document are included in Appendix 1 – B. References.

V. Clinical Review Methods

A. How the Review was Conducted

To support the efficacy of the new purified u-hFSH formulation, three clinical studies were submitted in electronic format on 29-Dec-03. The Sponsor originally used "purified Repronex® formulation" to represent the new formulation. The Sponsor changed the name from "purified Repronex® formulation" to "purified Menopur® formulation" in the 2003 submission.

- One clinical study conducted was titled: "An open-label, randomized, parallel group, comparative Phase III trial to study the efficacy and safety of HP Menotropin versus recombinant FSH administered subcutaneously to female patients in an IVF/ICSI program." This clinical study is identified as study MFK/IVF/0399E. The protocol for this study was never submitted to the FDA for review and the study was not originally intended to support approval for marketing in the U.S.
- A second clinical study conducted was titled: "A randomized, open-label, parallel group, multi-center, efficacy study comparing purified Repronex® SC, purified Repronex® IM and Repronex® SC in female patients undergoing in vitro fertilization". This clinical study is identified as study 2000-02.
- [redacted]

B. Overview of Materials Consulted in Review

This review contains direct reference to the original Medical Officer's Review of Repronex® dated 13-Aug-99. Previous clinical data obtained from the original NDA for the approved Repronex® product (NDA 21-047) were cross-referenced. (See Appendix 1 – A. Overview of clinical trials for NDA 21-047).
In addition, published literature references cross-referenced in this review are listed in a separate addendum (Appendix 1 – B. References).

C. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI audits for this NDA (21-663) found the three clinical studies acceptable.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Sample patient informed consent forms were submitted for the three clinical studies (2000-01, 2000-02 and MFK/IVF/0399E) and appear adequate. The Sponsor reported that the patient informed consent and investigator brochures were reviewed and approved by the relevant Institutional Review Board (IRB) or Independent Ethics Committee (IEC). In addition, the Sponsor included a list of the relevant IRB and IEC's for each clinical study.

E. Evaluation of Financial Disclosure

The financial disclosure statement (FDA 3454) for the new formulation of Menopur® (purified u-hFSH) has been completed for the two US clinical studies (2000-01 and 2000-02) and the European study (MFK/IVF/0399E) was reviewed by the Medical Officer and found to be acceptable.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The Sponsor's data from the U.S. in vitro fertilization study (2000-02) for the proposed Menopur® formulation (purified u-hFSH) given via the subcutaneous or intramuscular route failed to demonstrate clinical non-inferiority to approved gonadotropin formulations for the proposed ART indication in women [redacted]

However, it is also my opinion that the efficacy data obtained from Study MFK/IVF/0399E demonstrates non-inferiority of the subcutaneously-administered Menopur® (a European formulation) to an active comparator for the indication of multiple follicular development and pregnancy in ovulatory patients participating in an ART program. Based on acceptance of the bioequivalence study, Study MFK/IVF/0399E is acceptable to support the efficacy claim for Menopur® given subcutaneously for the indication of multiple follicular development and pregnancy in patients undergoing ART procedures.

B. General Approach to Review of the Efficacy of the Drug

Previously submitted data for the approved Repronex® formulation supported two indications in women: follicular development in an ART program and induction of ovulation (OI) in anovulatory infertile women. (See the original Medical Officer's review of NDA 21-047 dated 13-Aug-99) Clinical non-inferiority of the new Menopur® formulation (u-hFSH) was evaluated in three submitted clinical studies, two for the proposed ART indication, and one for the proposed [ ] The first two clinical studies were submitted to demonstrate efficacy of purified u-hFSH for the proposed indication in women undergoing ART (studies MFK/IVF/0399E and 2000-02). The third clinical study was submitted to demonstrate efficacy of purified u-hFSH [ ] [ ] (study 2000-01).

Repronex® (the progenitor compound) has [ ] indications of multiple follicular development and ovulation induction in patients who have previously received pituitary suppression. Follitropin alfa has similar indications of induction of ovulation and pregnancy in anovulatory patients and in the development of multiple follicles in the ovulatory patients participating in an ART program. The Sponsor conducted three clinical trials to assess the comparability of Menopur® to either Repronex® (2000-01 and 2000-02) or follitropin alfa (MFK/IVF/0399E).

Study MFK/IVF/0399E was submitted after the Sponsor reported in the pre-NDA meeting (03-Mar-03) that the initial U.S. study (2000-02) failed to meet the prespecified lower limit of the confidence interval for the purified Menopur® (u-hFSH) formulation administered subcutaneously for treatment in women undergoing assisted reproductive technologies (ART) Study MFK/IVF/ 0399E demonstrate the non-inferiority of a European formulation of the purified Menopur® (u-hFSH) to follitropin alfa (r-hFSH), administered subcutaneously. The clinical primary efficacy endpoint is the difference between the new purified u-hFSH administered subcutaneously and follitropin alfa (r-hFSH) in the clinical pregnancy rates.

Reviewer's comment on Study MFK/IVF/0399E: This study was submitted after preliminary analysis of study 2000-02 revealed that Menopur® administered subcutaneously did not meet the criteria for non-inferiority to Repronex® administered subcutaneously using an endpoint of total oocytes retrieved per cycle. The protocol for this study was never submitted to the FDA for review and the study was not originally intended to support approval for marketing in the U.S.

The Sponsor submitted study 2000-02 as support the first proposed labeling claim for the new purified Menopur® (u-hFSH) formulation administered intramuscularly for treatment in women undergoing assisted reproductive technologies (ART) using either in vitro fertilization (IVF).

Study 2000-02 was submitted to demonstrate non-inferiority for the new purified Menopur (u-hFSH) formulation administered either intramuscularly or subcutaneously to the currently approved Repronex® formulation. The clinical primary efficacy endpoint is the number of total oocytes retrieved per cycle.

Reviewer's comment on Study 2000-02: The Sponsor's analysis of study 2000-02 used a one-sided 95% confidence interval. The Division had informed the sponsor at a preNDA meeting on 03-Mar-03 that evaluation would need to be based on a two-sided 95% confidence interval. The Division's comparison of the lower bound of the two-sided 95% confidence intervals for Menopur® administered subcutaneously (-4.5) or intramuscularly (-4.3) to the approved Repronex® product failed to meet the prespecified lower bound of the confidence interval using the two-sided 95% confidence interval (-3.9), and therefore failed to meet the criteria for non-inferiority.

Reviewer's comment
1.

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C. **Detailed Review of Trials by Indication**

Study MFK/IVF/0399E

Study MFK/IVF/0399E began on May 1999 and was completed in November 2000.

Study title: "An Open-Label, Randomized, Parallel Group, Comparative Phase III Trial To Study The Efficacy And Safety Of HP Menotropin Versus Recombinant Human FSH (r-hFSH) Administered Subcutaneously To Female Patients In An IVF/ICSI program."

Investigator/Location: This study was conducted at 22 centers throughout Europe and Israel that enrolled at least one patient. Please refer to Appendix 1 – C. Principal investigator list.

Study rationale: The Sponsor stated the original rationale for this study was to evaluate the equivalence of the purified menotropin product with a recombinant FSH product (follitropin alfa).

Study objective(s): The Sponsor stated in the submission that the primary objective of this study was to compare the efficacy (in terms of ongoing pregnancy rates) of purified menotropin product to recombinant FSH, administered subcutaneously, in the treatment of females undergoing IVF and ICSI.

Reviewer's comment: The protocol and subsequent protocol amendments (labeled as Amendments 1, 2, and 3) for this IVF study (MFK/IVF/0399E) were not submitted to the Division for review. The effective dates for the protocol amendments were noted to be after the study had started. However, the protocol amendments were dated prior to the study completion. This reviewer noted the following current concerns in reading the protocol and protocol amendments for Study MFK/IVF/0399E:

Original Protocol: IVF and ICSI have different fertilization and pregnancy rates for patients with the diagnosis of male factor infertility. The Sponsor did not eliminate these male factor infertility patients from participating, and these patients may significantly alter the overall fertilization and pregnancy rates. Therefore, the results for IVF and ICSI will be evaluated separately.

There were two protocol amendments noted in the submission. The following key changes to the original protocol were noted:

1. **Protocol Amendment #1:**
   - **The Sponsor defined ongoing pregnancy as a patient with a positive fetal heartbeat ≥ 10 weeks after oocyte retrieval. The Division currently recommends that clinical pregnancy be the endpoint defined as a pregnancy 6 weeks post-embryo transfer.**
   - **The Sponsor broadened the type of gonadotropin-releasing hormone (GnRH) agonist (daily or depot), amount and route of administration of human chorionic gonadotropin (hCG) given for final follicular maturation, and luteal phase support (type and amount of progesterone) that would be used. This diversity in treatment protocols may have affected the final outcome.**
   - **The Sponsor added that down-regulation using a gonadotropin-releasing hormone agonist could be achieved if the Luteinizing Hormone (LH) level was < 5 mIU/mL following GnRH agonist injection. This method of assessing down-regulation is not acceptable in the United States.**
2. **Protocol Amendment #2**
   - **The Sponsor changed the primary objective from "comparing efficacy – in terms of ongoing pregnancy rates" to "demonstrating that highly purified menotropin is at least as efficient – in terms of ongoing pregnancy rates". This reviewer agrees that this study was designed to evaluate non-inferiority to a recombinant follicle stimulating hormone, not equivalence.**

Study design: Study MFK/IVF/0399E was an open-label prospective, randomized, multi-center, multi-national comparative study that recruited infertile women undergoing assisted reproductive technology procedures [either patients undergoing in vitro fertilization (IVF) or patients undergoing in vitro fertilization with intra-cytoplasmic injection (IVF/ICSI)].

Reviewer's comments: This study is not an optimal study for several reasons:

1. **there was a lack of blinding in this study, and raises the possibility that biases in assignment to treatment groups could have occurred.**
2. **the study used gonadotropin releasing-hormone agonists and progesterone products not available in the United States that may have effected the pregnancy outcomes.**

3. **in Germany, it is noted that there is a penal law prohibiting the transfer of more than 3 embryos and in the United Kingdom, there is a statutory regulation that limits the transfer of embryos to three. In contrast, in the U.S., the American Society of Reproductive Medicine (ASRM) has published guidelines[6]. The Society recommended increasing the number of embryos transferred based on the age of the patient.**
However, these ASRM guidelines are not enforceable. Therefore, the results of this study are clearly limited in attempting to draw conclusions that may be applicable to U.S. patients.

Method of assignment to treatment: Patients who met all of the inclusion/exclusion criteria were randomized into the two treatment groups. Subjects were randomized in a one-to-one ratio among treatment groups (Menopur® group or r-hFSH) prior to down-regulation with gonadotropin-releasing hormone agonist therapy.

The Sponsor further stated that randomization occurred in blocks by center and was stratified by method of insemination (in vitro fertilization [IVF] or intracytoplasmic injection [ICSI]). If a subject withdrew from the study prior to treatment completion, her treatment randomization number was not reassigned.

Patient population: The final protocol for study MFK/IVF/0399E stated that 720 patients were planned for enrollment to taking into account a dropout rate of 10%. The completed study randomized 781 patients, with a 727 receiving study treatment. The study treated 373 patients in the purified Menopur® group and 354 in the follitropin alfa group. There were 23 sites that participated, although only 22 sites enrolled patients.
The 22 sites included: 1 center in Belgium, 6 centers in Germany, 6 centers in Israel, 2 centers in the Netherlands, one center in Switzerland, and 6 centers in the United Kingdom. The contribution of patients from each site to study MFK/IVF/0399E varied from 10.2% (Centers 11 and 26 with seventy-four enrolled patients) to 1.4% (Center 62 with ten enrolled patients).

Reviewer's comments:

1. **The Sponsor also noted that 54 subjects (7% of total randomized patients including 22 patients [5.6%] in the Menopur® group and 32 patients [8.3%] in the r-hFSH group) were dropped-out prior to the start of the study drug. No details on the reason for discontinuation were given for 26 of these subjects.**

   The Sponsor did report that some of the reasons included spontaneous pregnancy, withdrawn consent, and sperm problems. Although this is not optimal, it is well under the Division's concern level of a drop-out rate over 10%, and under the most recent (2001) US data that quoted a drop-out rate for Assisted Reproductive Technology patients undergoing therapy of 11.3%[7].

2. **The Sponsor also reported that three patients received both study medications and were excluded from the ITT analysis. In this reviewer's opinion, exclusion of these patients is acceptable.**

Key inclusion criteria:

1. Female patients with infertility period > 1 year, except for proven bilateral tubal occlusion and/or male factor
2. Eligible for IVF/ICSI
3. A minimum of one menstrual cycle without treatment with fertility modifiers prior to the pre-study examination
4. Patients aged 18-38 years with regular menstrual cycles of 24-36 days, documented by early/mid-luteal phase progesterone levels of > 10 ng/mL
5. Ultrasound prior (within the last 12 months) to or at pre-study examination showing presence of both ovaries, without evidence of clinically relevant abnormalities (e.g. PCOS), normal uterus and adnexa
6. Clinically normal baseline parameters for hematology, blood chemistry, urinalysis (dip-stick) within the last 12 months
7. Baseline endocrine determinations, all values within the normal limits for the clinical laboratory, within the last 12 months

Key exclusion criteria:

1. Presence of any clinically relevant systemic disease (e.g. insulin-dependent diabetes), endocrinological disorders or ovarian cysts which preclude IVF/ICSI procedures
2. More than three previously unsuccessful IVF/ICSI cycles (i.e. not resulting in an ongoing pregnancy)
3. BMI < 18.0 and > 29.0 kg/m^2
4. Patient regularly smokes more than 10 cigarettes a day
5. Diagnosed as "poor responder" in gonadotropin-stimulated procedures ("poor response" is defined as development of less than 4 follicles and/or more than 20 days of gonadotropin stimulation until human chorionic gonadotropin (hCG) criteria met
6. History of severe ovarian hyperstimulation (OHSS) type III in former hormonal ART treatment
7. Participation in any study of any investigational drug within the last 30 days

Trial period: From May 1999 through November 2000.

Dosage and Administration:

The protocol for dose initiation and adjustment was:

- Patients in the Menopur® formulation treatment group (administered subcutaneously) -- the starting dose was a fixed 225 IU (3 vials) per day for 5 days, then could be adjusted by the investigator on cycle day 6 up to a maximum of 450 IU per day or down to a minimum of 75 IU per day. Treatment duration with gonadotropin was limited to ≤ 20 total days.
- Patients in the r-hFSH formulation treatment arm – the starting dose was 75 IU sc daily. the starting dose was a fixed 225 IU (3 vials) per day, then could be adjusted by the investigator on cycle day 6 up to a maximum of 450 IU per day or down to a minimum of 75 IU per day. Treatment duration with gonadotropin was limited to ≤ 20 total days.

Treatment protocol: Patients who met the inclusion/exclusion criteria were randomized and began treatment with a gonadotropin-releasing hormone (GnRH) agonist during the mid-luteal phase (either daily or depot administration) to achieve pituitary down-regulation.

Pituitary down-regulation was defined as a serum estradiol level ≤ 200 pmol/L and serum LH level < 5 mIU/mL and/or ultrasound (to exclude ovarian cysts) after gonadotropin-releasing hormone agonist treatment. In eligible patients, once the down-regulated serum hormonal level(s) had been achieved, gonadotropin therapy with either Menopur® or r-hFSH was initiated 10-17 days after initial GnRH agonist administration. The first day of gonadotropin therapy was designated as cycle day 1.

Gonadotropin and gonadotropin-releasing hormone agonist therapy (using daily or depot) were continued until:

- The patient had a poor response defined as < 4 follicles on ultrasound and/or overall stimulation period with gonadotropins > 20 days.
- The patient was felt to be at risk of ovarian hyperstimulation syndrome as determined by the investigator and treatment was withdrawn.
- The patient met the criteria for human chorionic gonadotropin [hCG] (5,000 IU to 10,000 IU administered subcutaneously or intramuscularly) was met.

Reviewer's comment: The criteria for removal of a subject for OHSS from this study were an estradiol of 12,000 pmol/L (approximately 3,333 pg/mL) or > 25 follicles of > 12 mm. This occurred in 9 patients (2%) of patients using Menopur® and 6 patients (2%) of patients using follitropin alfa. Although the stimulation protocols used in Europe are slightly lower than the rate quoted in the United States (3.5%)[7], in this reviewer's opinion, these cancellations for ovarian hyperstimulation appear acceptable.

The criteria for administering hCG was:

- ≥ 3 follicles on ultrasound with each having a diameter of ≥ 16 mm

and/or

- Serum estradiol levels ≥ 1,000 pmol/L (approximately 278 pg/mL) per 16 mm follicle

Oocytes were retrieved approximately 32-42 hours after hCG administration (5,000-10,000 IU); oocytes were retrieved, assessed and fertilized using IVF or ICSI. No more than 3 embryos were replaced. Oocyte, embryo and final outcome assessments were made for all patients. Luteal phase support was progesterone administered from commercial lots beginning within three days of ovulation induction and until a negative serum pregnancy test. If the serum pregnancy test was positive, progesterone was continued until a negative serum pregnancy test, or until a fetal heartbeat was confirmed.

Reviewer's comments:

- **The Sponsor did not require early serum follicular FSH, LH and estradiol levels to be normal prior to entry. It is possible that some patients in this European group would not have qualified for ART treatment in the United States as the cut-off FSH levels for clinical treatment in the US range from 10-15 mIU/mL. Therefore, the actual patient populations (and results) in the European centers may not be directly comparable to those seen in the US.**
- **The Sponsor did not standardize luteal replacement with progesterone between centers. As there have been no head-to-head comparison trials of progesterone drug products for luteal phase replacement, it is unknown whether this may have caused some variation in pregnancy rate between centers.**
- **The Sponsor did not standardize the GnRH agonist or dose used. This reviewer notes that two depot preparations were used (Decapeptyl® and Zoladex®) and four daily preparations (Decapeptyl®, buserelin, leuprolide acetate and Synarel®). It is unknown whether the differences in GnRH agonists had an effect on clinical outcomes, since the study was not stratified for these different agonists. This reviewer notes that five of the six gonadotropin-releasing hormone agonists used in this study (Decapeptyl®, Zoladex®, buserelin, and Synarel®) do not have an indication for down-regulation for ART stimulation protocols in the United States.**

Demographic and baseline characteristics:

Treatment groups were similar with respect to most baseline characteristics for the Menopur® and r-hFSH treatment arms. Demographic and baseline characteristics are reported in Appendix 2 – Tables 1A, and 2A.

Demographic and baseline characteristics included:

- Mean patient age was 30 years in Menopur® and r-hFSH treatment arms.
- Mean BMI was 23 kg/m^2 in the Menopur® and r-hFSH treatment arms.
- A similar racial profile for study MFK/IVF/0399E in both the Menopur® and r-hFSH treatment arms.
- The occurrence of the primary cause of infertility was clinically equivalent between the three treatment groups.

Other treatment parameters reported in Appendix 2 – Table 3A include:

- The distribution of patients receiving daily compared to depot gonadotropin-releasing hormone agonist was approximately equal between the groups.
- The distribution of patients receiving ICSI for insemination was approximately double the number of patients undergoing regular IVF.

Reviewer's comments:

1. **The use of different gonadotropin agonists (depot as compared to daily) in the two treatment groups may have altered the overall pregnancy rates. However, it is unlikely to alter the comparison between treatment groups, since the distribution between these two formulations of gonadotropin-releasing hormone agonist appears to be approximately equal between the two groups (See Appendix 2 – Table 2A).**
2. **It is important to note that the number of patients undergoing ICSI was twice the number of patients undergoing IVF. Pregnancy rates for male infertility are much higher with ICSI, especially with epididymally retrieved sperm fertilization (i.e. severe male factor)[8].**
3. **No semen analysis parameters or source of sperm were reported for any of the treated patients.**
   As over 65% of patients in this study had male factor infertility, it is unknown if inclusion of patients who had severe male factor would have generated a statistical imbalance between the two treatment groups.
4. **No patient data is available regarding past background obstetric and gynecologic history including: parity, abortions, previous ectopic pregnancies and previous number of IVF (IVF/ICSI) cycles. Since prior pregnancy is a significant predictor of those likely to conceive with gonadotropin drug products, it is important that any study of these drug products for the purpose of achieving pregnancy collect and report this information.**

Down-regulation parameters (Serum estradiol levels on Day 1 of gonadotropin stimulation) are reported in Appendix 2 – Table 4A:

- Mean serum estradiol levels on cycle day 1 were clinically similar between the two treatment groups overall, although with wide ranges.

- Mean serum estradiol levels on cycle day 1 were clinically similar between those using daily GnRHa and depot GnRHa in the two treatment groups when stratified by method of insemination.

Reviewer's comment: The Sponsor noted that seven patients in the Menopur® group and three patients in the r-hFSH group had serum down-regulated serum estradiol values above the stated threshold of ≥ 200 pmol/L (approximately 56 pg/ml) on cycle day 1.
However, a recent small study noted that there did not seem to be significant differences in outcome between patients who did not achieve significant down-regulation[9]. In this reviewer's opinion, there is very limited evidence to predict who is appropriately down regulated, and what impact the lack of down-regulation has on cycle outcomes.

Primary efficacy assessment for study MFK/IVF/0399E:

The primary efficacy endpoint designated by the Sponsor was the ongoing pregnancy rate after one treatment cycle. Ongoing pregnancy rate was defined as a pregnancy with a positive fetal heart rate ≥ 10 weeks after oocyte retrieval.

The Sponsor designated multiple secondary efficacy endpoints including:

- Follicles (as measured on ultrasound)
- Oocytes retrieved
- Oocytes fertilized
- Embryos transferred
- Patients with biochemical pregnancies (positive serum β-hCG values)
- Patients with clinical pregnancies (positive heart action ≥ 4 weeks post-oocyte retrieval)
- Days of stimulation with gonadotropins
- Vials/ampules used

Protocol violations and other allocation issues:

Total allocation - Study MFK/IVF/0399E randomized 781 patients to the two treatment groups. The ITT population who were treated with at least one dose of study medication included 727 patients of whom 700 (96.3%) had an oocyte retrieval.

The Sponsor reported that the allocation of patients in the two primary efficacy treatment arms appeared to be clinically similar (See Appendix 2 – Table 5A)

The number and percentage of patients having oocyte retrieval included:

- 361 (96.8%) of patients in the Menopur® group
- 339 (95.8%) of patients in the r-hFSH group

The number and percentage of patients receiving an embryo transfer included:

- 336 (90.1%) of patients in the Menopur® group
- 315 (89.0%) of patients in the r-hFSH group

Reviewer's comments: It is not surprising that the number of patients having ICSI outnumbered the patients undergoing IVF by a two to one ratio since a majority of the patients (over 65% in both treatment groups) had a primary diagnosis of male infertility (See Appendix 2 – Table 2A). The effects including patients with intracytoplasmic injection (ICSI) on pregnancy rates should have been planned in the initial statistical analyses. The inclusion of these patients makes it difficult to compare the outcomes to Study 2000-02, which excluded these ICSI patients.

Protocol violations – A significant number of patients (59%) had protocol violations in the intent-to-treat population. The number of patients with violations appeared to be roughly equivalent between the two treatment groups (220 protocol violations in the Menopur® group and 210 in the r-hFSH group)

Reviewer's comments: The exact number of protocol violations that occurred after randomization included: lacking normal laboratory values at entry, lacking a normal screening ultrasound at entry and/or regular cycles. In this reviewer's opinion, the overall effect of these violations is unknown, but these violations appear to be roughly equally distributed between the treatment groups (See Appendix 2 – Table 6A). This reviewer had significant concerns with reference to twelve patients who completed therapy that included:

- **8 patients who were randomized to IVF or ICSI, and were treated with a different method of insemination from the one originally planned.**
- **4 patients that had mixed inseminations (oocytes treated with IVF and oocytes treated with ICSI from the same patient).**
- **8 patients used of Choragon® (an overseas formulation of human chorionic gonadotropin) for the luteal phase support (as compared to the standard progesterone regimen)**

In this reviewer's opinion, since these patients represented less than 2% of the treatment arms, the effect of this on the final outcome of pregnancy is unknown, but probably small. However, the overall number of protocol violations (430) appears to be a significant number; although the actual contribution of these protocol violations (as most appeared to be failure to meet inclusion criteria) is unknown. This reviewer notes that overall protocol violations appeared to be equally distributed in both number and types of violations between the two efficacy treatment groups (See Appendix – Table 6A for the Key Protocol Violations) and in this reviewer's opinion, were minor except for the 20 patients mentioned above. Therefore, the ITT patient population appeared to be acceptable although not optimal.

In addition, this reviewer also notes that the ITT population in this study is different from the ITT population in study 2000-02 (the US IVF study) because this EU study has significantly higher discontinuation and protocol violation rates (as a consequence, the US study was more selective). Therefore, besides the obvious difference in primary efficacy endpoints, a direct comparison between studies MFK/IVF/0399E and study 2000-02 cannot be made because of the significant differences in patient selection.

Primary efficacy evaluation for Study MFK/IVF/0399E:

The Sponsor's designated primary efficacy endpoint was the clinical pregnancy rate. In order to compare the clinical pregnancy rate between the two treatment groups (Menopur® and r-hFSH), the ITT population was analyzed. The ITT population was defined as patients that received at least one dose of gonadotropin and included 727 patients. (See Appendix 2 - Table 7A).

Three patients were excluded from the ITT analysis as they received both gonadotropin medications.

The Sponsor's reported ongoing clinical pregnancy rate for patients in the ITT group included:

- 87 patients in Menopur® group (23.3%)
- 73 patients in the r-hFSH formulation group (20.6%)

The Sponsor's analysis plan stated that if the lower limit of the two-sided 95% confidence interval for overall clinical pregnancy was greater than the non-inferiority limit (-10%), then the null hypothesis would be rejected and Menopur® will be considered non-inferior to r-hFSH. The Sponsor's Statistical analysis shows that the lower bound of the two-side 95% confidence interval of the difference between the two treatment groups [Menopur® minus r-hFSH] was greater than -10%, and therefore non-inferiority was demonstrated. (See Appendix 2 - Table 7A). The two-sided 95% confidence interval that the Sponsor calculated was [-3.3, 8.7] with ongoing pregnancy rates of 23% and 21% in the Menopur® and r-hFSH groups, respectively.

Reviewer's comments:

1. **The Division's analysis of the data for Study MFK/IVF/0399E reveals similar pregnancy rates and confidence intervals (See Appendix 2 – Table 7A). In the Division's analysis, the two-sided 95% confidence interval was [-2.4%, 9.7%], which still is within the Sponsor's prestated non-inferiority limit of -10%.**
2. **The Division performed two secondary analyses of the primary efficacy endpoint stratified by the type of insemination (*in vitro* fertilization [IVF] or intra-cytoplasmic injection [ICSI]) and by the type of gonadotropin-hormone releasing agonist (GnRHa).**

These two analysis consistently showed a greater pregnancy rate for the Menopur® groups compared to r-hFSH. (See Appendix 2 – Table 7A), although all of these analyses consistently showed non-inferiority between the two treatment groups.

The Division's analysis demonstrated that:

- **The modified ITT analysis with stratification by insemination type revealed that the lower bound of the confidence interval of the difference in the ongoing pregnancy rate was greater than -10% for Menopur® SC compared to r-hFSH for IVF and ICSI, respectively.**
- **The modified ITT analysis with stratification by gonadotropin agonist revealed that the lower bound of the confidence interval of the difference in the ongoing pregnancy rate was greater than -10% for Menopur® compared to r-hFSH for depot gonadotropin releasing hormone agonist use and daily gonadotropin releasing hormone agonist use, respectively.**
- **In examining the point estimates from a clinical standpoint, it appears that the IVF group treated with r-hFSH had a somewhat lower pregnancy rate (22 subjects - 19.8%) compared to the IVF group treated with Menopur® (37 subjects - 30.5%), although the differences were not as apparent in the ICSI treated groups (53 subjects - 22.1% and 49 subjects - 22.4%), respectively. The reason for the disparity between the two IVF treated groups is unknown. However, in this reviewer's opinion, this disparity did not appear to clinically impact the overall study outcome.**

Key secondary efficacy parameters:

A. The livebirth rate for patients in the ITT group (see Appendix 2 – Table 8A) included:

   - 80 patients in Menopur® group (21.4%)
   - 67 patients in the r-hFSH formulation group (18.9%)

B. Treatment exposure was clinically similar for the two treatment groups

Overall Results for Treatment Exposure

	Menopur® group	r-hFSH group
Mean number of ampules (total)	36.9	37
Mean duration of treatment (days)	11.5	11.5

Source: Sponsor's submission NDA 21-663/Volume 30/Tables 11 and 13

Reviewer's comment: No clinical differences were noted in patient exposure in terms of the mean number of ampules required or duration of use between the treatment groups (Menopur® and r-hFSH).

Study 2000-02

Study 2000-02 began on September 2000 and was completed April 2001.

Study title: "A Randomized, Open-label, Parallel-group, Multi-center, Efficacy Study Comparing Purified Repronex® SC, Purified Repronex® IM And Repronex® SC In Female Patients Undergoing In-Vitro Fertilization."

Reviewer's note: (The tradename purified Repronex® has been changed to Menopur®)

Investigator/Location: This study was conducted at 15 centers in the United States that enrolled at least one patient. Please refer to Appendix 1 – D. Principal investigator list.

Study rationale: The stated rationale was to assess the therapeutic efficacy, safety, and tolerance of purified Repronex® (now Menopur®) using the subcutaneous or intramuscular route and compared to Repronex® (the currently approved menotropin product) subcutaneously in female patients undergoing in vitro fertilization (IVF).

Study objective(s):

1. Purified Repronex® (now Menopur®) administered subcutaneously or intramuscularly will demonstrate statistically comparable therapeutic efficacy for the primary outcome variables to Repronex® administered subcutaneously.
2. Purified Repronex® (now Menopur®) subcutaneously or intramuscularly will demonstrate equivalent safety and better local tolerability than Repronex® subcutaneously (the current approved menotropin product)

Study design: Study 2000-02 was an open-label prospective, randomized, multi-center, comparative study performed in the United States that recruited infertile women undergoing in vitro fertilization (IVF).

Reviewer's comments:

The protocol for study 2000-02 was submitted to the Division for review on 02-Oct-00 (IND 53,954/Serial number 007-PN). At that time, the original protocol was reviewed, and was signed off by the Medical Officer. In this reviewer's opinion, this protocol would not have met the Division's current design recommendations for ART studies because:

- **The study was an open-label study as opposed to a double-blinded study. This methodology could have potentially resulted in bias in allocating patients into treatment groups.**
- **The study used total oocytes as a primary efficacy endpoint.**

"Modification #1" (submitted to IND 53,954/Serial No. 011-IM) changed the stated delta for study 2000-02 from 1.2 oocytes to 3.9 oocytes as the clinically meaningful difference in the test for non-inferiority of Menopur® to Repronex® (a clinical difference agreed to by the Division in a letter dated 12-Oct-01). In this reviewer's opinion, published literature does not show that a difference of 3.9 total oocytes retrieved constitutes a significant clinical difference between treatment groups.

Method of assignment to treatment: Patients who met the inclusion/exclusion criteria were randomized upon confirmation of pituitary down-regulation, immediately prior to the start of gonadotropin. Patients were randomly assigned to one of three treatment groups according to randomization codes provided by the Sponsor. If the patient met these criteria, she was considered down-regulated and was randomized (in a 1:1:1 ratio) to one of three treatment arms: Menopur® formulation (administered subcutaneously [SC]), Menopur® formulation (administered intramuscularly [IM]) or the approved Repronex® formulation (administered SC). If a subject withdrew from the study prior to treatment completion, her treatment randomization number was not reassigned. The Sponsor stated that randomization was stratified by center.

Patient population: The final protocol for study 2000-02 stated that 225 patients were planned for screening to enroll 180 evaluable patients taking into account a dropout rate of 20%. The completed study randomized a total of 199 patients, with a 190 receiving study treatment. The study treated 65 patients in the intramuscularly administered Menopur® arm, 61 patients in subcutaneously administered Menopur® arm and 64 patients in the approved Repronex® arm. There were 15 sites in the United States with the contribution of patients from each site to study 2000-02 varying from 12% (23 patients enrolled at Center 8) to 2.6% (5 patients enrolled at Centers 10 and 11 per center).

Reviewer's comment: This study was designed differently than study MFK/IVF/0399E in that patients were not randomized until after confirmation of down-regulation. This protocol design contributed to a significantly lower drop-out rate (4.5%) compared to study MFK/IVF/0399E (7%). Nine patients in this study were enrolled and not randomized. Three patients withdrew consent, two failed to down-regulate, two had an adverse event prior to randomization, one was disqualified by the Sponsor and one became pregnant.
Although this failure to randomize was noted in 4.5% of the patient population, no significant disparity in distribution of patients between treatment groups was noted. In addition, this study reached its goal of a sample size of 60 patients per group as stated in the original treatment protocol.

Duration of clinical treatment: Patients undergoing an assisted reproductive technology cycle with in vitro fertilization could be treated for one cycle only.

Key inclusion criteria:

1. Premenopausal females between 18 and 39
2. Nonsmokers
3. Regular ovulatory menstrual cycles of 24 to 35 days
4. Evidence of one of the following within 90 days of leuprolide acetate treatment
    a. Mid-luteal serum progesterone level > 5 ng/mL or
    b. Late luteal phase endometrial biopsy < 3 days lag or
    c. Biphasic basal body temperature charts or
    d. Mid-cycle urinary LH surge
5. Early follicular phase (day 2-3, preferably day 3) serum estradiol (E2), luteinizing hormone (LH), follicle stimulating hormone (FSH) , prolactin (PRL), testosterone (T), dehydroepiandrosterone sulfate (DHEAS), within the normal limits for the clinical laboratory, or considered not clinically significant by the investigator.
6. Thyroid stimulating hormone (TSH) within normal limits for the clinical laboratory or considered not clinically significant by the investigator within 90 days prior to leuprolide acetate treatment.
7. Clinically normal baseline hematology, chemistry, and urinalysis values within 90 days prior to leuprolide acetate treatment
8. Documented history of infertility for at least one year attributable to or in association with tubal factor, endometriosis (Stage I or II only at the time of screening), or unexplained causes at screening. Patients with severe tubal damage at least three months prior to screening are eligible for enrollment. C Couples with an associated male factor may be enrolled only if donor sperm is used.
9. Male partner (within 6 months prior to baseline visit) semen analysis showing normalcy.
10. Presence of both ovaries without evidence of clinically significant abnormality as detected by vaginal ultrasound performed prior to baseline visit
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. Hysterosalpingography, hysteroscopy, or sonohysterogram documenting a uterine cavity consistent with expected normal function within the previous three years prior to baseline visit

Key exclusion criteria:

1. Presence of any clinically relevant systemic disease
2. A body mass index of greater than 34 kg/m^2
3. More than three previous ART cycles prior to screening

4. 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 ≤ 2 mature follicles or history of 2 previous cycle cancellations prior to oocyte retrieval due to poor response.
5. Active or prior history of substance abuse, including alcohol or tobacco
6. History of chemotherapy or radiotherapy
7. For male partner, obvious leukospermia (> 2 million WBC/mL) or signs of infection in semen sample within the past two months
8. Participated in any experimental drug study within 60 days prior to screening for this study

Reviewer's comment: This reviewer has concerns that the inclusion criteria stated that semen analysis needed to be essentially "normal", but 9 patients (5%) had a primary infertility diagnosis of "male infertility".

Trial period: From September 2000 through April 2001.

Dosage and administration:

The protocol for dose initiation and adjustment with gonadotropin:

- Menopur® formulation treatment groups (administered subcutaneously or intramuscularly) -- the starting dose was fixed at 225 IU (3 vials) per day sc for the first four days. On cycle days 5 through 12, the dose could be adjusted up to a maximum of 450 IU per day or down to a minimum of 75 IU per day. Treatment duration with gonadotropin was limited to ≤ 12 days.
- Repronex® treatment group – the starting dose was fixed at 225 IU (3 vials) per sc. sc for the first four days. On cycle days 5 through 12, the dose could be adjusted up to a maximum of 450 IU per day or down to a minimum of 75 IU per day. Treatment duration with gonadotropin was limited to ≤ 12 days.

Treatment protocol:

Patients who met the inclusion/exclusion criteria began treatment with subcutaneous leuprolide acetate (a gonadotropin-releasing hormone agonist) (1 mg daily) for a maximum of 20 days prior to gonadotropin start. Pituitary down-regulation was continued until the onset of menses and until the serum estradiol level was ≤ 45 pg/mL and the endometrial thickness was ≤ 7mm on ultrasound measurement. Leuprolide acetate treatment was initiated 7 days before the anticipated onset of the second menstrual cycle for a maximum of twenty days.

Following initiation of leuprolide, patients could schedule an appointment for a study visit within seven days after the start of their menstrual period on leuprolide (any patient that did not have a menses on leuprolide therapy by 20 treatment days was withdrawn from the study). At the study visit, an ultrasound was used to confirm that the patient did not have pre-existing ovarian cysts or follicles. If down-regulation was achieved (by the criteria stated previously), the patient was randomized and gonadotropin therapy with either Menopur® or Repronex® was initiated. The first day of gonadotropin therapy was considered cycle day 1. Daily gonadotropin (Menopur® or Repronex®) treatment and gonadotropin-releasing hormone agonist (leuprolide acetate) therapy was continued and adjusted as documented in the Dosage and Administration section until:

1. A patient was documented to have a "poor response" as defined by the absence of a clinically significant rise in serum estradiol levels following three consecutive treatment days at the maximum dose (450 IU) of Menopur® or Repronex®.
2. A patient was felt by the investigator to be at risk for ovarian hyperstimulation (OHSS) or a serum estradiol level of 6,000 pg/mL
3. A patient was documented to have a clinically significant decline in serum estradiol levels for two consecutive determinations.
4. The criteria for human chorionic gonadotropin [hCG] (10,000 IU administered intramuscularly) were met (or hCG could be delayed up to 3 days after the last gonadotropin dose for "coasting").

Reviewer's comment: The criteria for removal of a subject for OHSS from this study included an estradiol of 6,000 pg/mL which was twice the level required for cancellation in the European study (approximately 3,333 pg/mL) MFK/IVF/0399E. In addition, the criteria for removal in this study used ovarian diameter of > 12 cm as opposed to follicular number. In this study only one patient (0.5%) in this US study was removed after developing moderate OHSS (in the Repronex® IM group), and no patients were removed for this risk of OHSS. This number is clinically lower than the rate quoted in the United States (3.5%)[7], and reflects the small patient population studied. This illustrates one of the many difficulties in attempting to compare ART studies in Europe to those in the United States.
In this reviewer's opinion, no trend of overaggressively canceling patients for the risk of OHSS occurred in either study.

The criteria for administering hCG were:

- ≥ 3 follicles on ultrasound with each having a diameter of ≥ 16 mm

and/or

- Serum estradiol levels were appropriate for the number of follicles observed based on the investigator's clinical judgment

Oocytes were retrieved approximately 34-36 hours after hCG administration, oocytes were be retrieved, assessed and fertilized using IVF. ICSI and assisted hatching procedures were not allowed. No more than 4 embryos were replaced at the time of embryo transfer. Oocyte, embryo and final outcome assessments were made for all patients. Luteal phase support was daily progesterone administration in the form of 8% Crinone® gel at a 90 mg daily dose vaginally beginning on day 2 to 3 of oocyte retrieval until a negative serum pregnancy test. If the serum pregnancy test was positive, Crinone® was continued until a negative serum pregnancy test, or until a fetal heartbeat was confirmed.

Reviewer's comment: It is important to note that there were several protocol treatment differences (in addition to different criteria for cancellation for OHSS) between Study 2000-02 and Study MFK/IVF/0399E. These differences include:

- **An inclusion requirement for a normal follicular FSH and estradiol level in Study protocol 2000-02, not present in MFK/IVF/0399E.**
- **An exclusion of male partners with leukospermia or signs of infection in the semen sample within the past two months in study 2000-02, not present in MFK/IVF/0399E**
- **The use of a different GnRH agonist in 2000-02 (leuprolide acetate) and study MFK/IVF/0399E**
- **The use of different serum criteria defined as adequate down-regulation between studies 2000-02 (Serum estradiol of 45 pg/ml) compared to study MFK/IVF/0399E (Serum estradiol of 56 pg/mL).**
- **The required use of Crinone® (a vaginal progesterone gel) as luteal phase support in study 2000-02 compared to the choice of progesterone for luteal phase support being left to the individual investigator in study MFK/IVF/0399E.**

In this reviewer's opinion, these differences reflect treatment differences between the U.S. and the EU ART. These fundamental differences in treatment protocols, termination criteria and possibly media and embryo catheter differences questions the generalizability of studies conducted outside the U.S. to patients undergoing ART treatment here.

It is also difficult to assess the impact of these differences without designing the study to include stratifying by country. This would allow the study to reflect the potential differences in ART pregnancy rates in each country.

Demographic and baseline characteristics:

Treatment groups were similar with respect to most baseline characteristics for the Menopur® subcutaneous, Menopur® intramuscular and Repronex® treatment arms. Demographic and baseline characteristics are reported in Appendix 2 – Tables 1B, and 2B and include:

- Mean patient age was 32 years in both the Menopur® subcutaneous and Repronex® treatment arms. Mean patient age in the Menopur® intramuscular group was 31.6 years.
- Mean BMI was 24 kg/m^2 in the three treatment groups: Menopur® subcutaneous, Menopur® intramuscular and Repronex® treatment arms.
- The occurrence of the primary diagnosis for infertility and number of previous cycles of infertility was not clinically different between the treatment groups.
- Review of the obstetrics and gynecologic history in the three treatment groups included: previous gonadotropin cycles, prior full terms births and prior abortions showed did not demonstrate overall significant imbalances in these characteristics between treatment groups.

Reviewer's comments:

1. **The approved Repronex® group had a smaller proportion of patients who were African-American (one patient - 1.6%) compared to the other two treatment arms (7 in the Menopur® subcutaneous arm and 9 patients in the Menopur® intramuscular arm - approximately 12% per arm). The imbalance in racial characteristics in the three treatment arms is concerning, although the effects of this imbalance on oocyte retrieval parameters are unknown. However, this reviewer notes that published literature may suggest that there may be varying responses to gonadotropins in different ethnic groups[10].**
2. **The distribution of patients with previous ectopic pregnancies was greater in the Menopur® IM group (15 patients) compared to the other two groups (9 in the Menopur® SC group and 8 in the Repronex® SC group). In addition, there were no patients in the Menopur® SC group with more than 2 abortions, compared to 5 patients in each of the other two treatment groups). The effects of these imbalances are unknown. However, in this reviewer's opinion, these imbalances are unlikely to impact the primary efficacy outcome of number of oocytes retrieved in this study.**

Down-regulation parameters (Serum estradiol levels on Day 1 of gonadotropin stimulation):

The mean follicular stimulating hormone (FSH) levels at baseline and serum estradiol levels at downregulation (Day 1 of gonadotropin administration) were similar between the three treatment groups (See Appendix 2 - Table 3B).

Reviewer's comments: The ranges of down-regulated estradiol levels included values up to 283 pg/mL. The protocol stated that a down-regulated estradiol was to be ≤ 45 pg/mL. This reviewer has noted that 38.9% of patients had serum estradiol levels greater than 45 pg/mL. The impact of a lack of down-regulation on the primary efficacy parameter is unknown. However, approximately 30% of patients in study 2000-02 were over 35. One article suggests that a lack of down-regulation may be of greater significance on outcome measures in this older age group as compared to patients under 35[11], although the actual effect on the clinical outcome of a lack of down-regulation is unknown.

Primary efficacy assessment for study 2000-02:

The primary efficacy endpoint designated by the Sponsor was the number of oocytes retrieved per cycle.

The Sponsor designated multiple secondary efficacy endpoints including:

- Peak serum estradiol levels
- Percentage of cycles with oocyte retrieval
- Percentage of cycles with embryo transfer
- Percentage of cycles with chemical pregnancies (positive β-hCG values)
- Percentage of cycles with clinical pregnancies (defined as an ultrasound with a gestational sac)
- Percentage of cycles with continuing pregnancies (defined as an ultrasound with a fetal heart motion)

Protocol violations and other allocation issues:

Total allocation - Study 2000-02 randomized 190 patients to the three treatment groups. The ITT population, patients who were treated with at least one dose of study medication, included all 190 patients of whom 185 (97% of the ITT population) had an oocyte retrieval.

In the three primary efficacy treatment arms, the number of patients undergoing embryo transfer was similar between treatment groups (See Appendix 2 – Table 4B).

Protocol violations - The Sponsor reported that the primary efficacy analysis included 25 patients who completed therapy despite violations of the protocol for this ART study.

Reviewer's comments: The reviewer concurs that 23 of the 25 patients had "Key" protocol deviations - see Appendix 2 – Table 5B. Two patients had a failure of characterization of the morphology of donor sperm, which is in this reviewer's opinion a very minor deviation.

Although fertilization was not a primary endpoint, seven patients that had "rescue ICSI" (3.7%) present the most concerning protocol deviation. Overall the protocol violations appear to be equally distributed between treatment groups, and this reviewer agrees with the Sponsor that these violations probably did not affect the overall outcome of the study. However, the Sponsor reported numerous "minor deviations" that were not listed in the study report including results of semen analysis, down-regulated estradiol levels, and time of screening procedures. It is unknown whether these non-reported protocol violations were evenly distributed or whether unequal distribution may have influenced the outcome of this study. However, this reviewer agrees that most of the violations appear to be "minor" and, therefore, may not have altered the overall outcome.

Primary efficacy evaluation for Study 2000-02:

The Sponsor's designated primary efficacy endpoint was total oocytes retrieved per cycle. In order to compare the total oocytes retrieved between the three treatment groups (Menopur® SC, Menopur® IM and the approved product Repronex® SC), the ITT population was analyzed. The ITT patient population was defined as 190 total patients that received at least one dose of gonadotropin. (See Appendix 2 - Table 6B).

The ITT total oocytes retrieved rate was:

- 13.1 total oocytes in the Menopur® formulation administered subcutaneously (SC) group
- 13.1 total oocytes in the Menopur® formulation administered intramuscularly (IM) group
- 14.4 total oocytes in the Repronex® formulation administered (SC) subcutaneously group

The original protocol and Modification #1 (dated 12/1/2000) state: "Ninety-five (95%) confidence intervals will be calculated for the efficacy outcomes for each treatment and compared". The Sponsor also stated that a delta of 3.9 oocytes was a clinically meaningful difference for non-inferiority between the Menopur® groups and Repronex® SC.

Reviewer's comments:

1. **The protocol and the modification never explicitly state whether a two-sided or one-sided 95% confidence interval would be used. In fact, the discussions of sample size calculations imply one-sided 97.5% confidence intervals using Dunnett's procedure to adjust for two comparisons with Repronex® SC would be used. In addition, the Sponsor was informed at the preNDA meeting that the Division would evaluate the data using a two-sided 95% confidence interval for non-inferiority testing.**

Therefore, this reviewer will analyze oocyte data using a two-sided 95% confidence interval adjusted for Dunnett's procedure.

2. **The Division's analysis of the data demonstrates that the lower bound of the two-sided 95% confidence intervals of the difference between Menopur® given either subcutaneously (-4.5) or intramuscularly (-4.3) vs. Repronex® SC does not exclude a difference greater than 3.9 oocytes in favor of Repronex® SC (See Appendix 1 – Table 6B). In this reviewer's opinion, this demonstrates that the Menopur® formulations (given SC or IM) _demonstrate a lack of efficacy using the prespecified endpoint of total oocytes as a surrogate marker. Similar results (n=183) were obtained when removing patients who underwent "rescue ICSI" (Results not shown).**

Key secondary efficacy parameters:

A. The clinical pregnancy rate in the ITT population included (See Appendix 2 – Table 7B):

- 18 patients in the Menopur® SCgroup (29.5% per attempt)
- 25 patients in the Menopur® IM group (38.5% per attempt)
- 24 patients in the Repronex® SC group (37.5% per attempt)

B. Treatment exposure was not significantly different ($p<0.01$) between treatment groups.

Overall Results for Treatment Exposure

	Menopur® SC	Menopur® IM	Repronex® SC
Mean dose/total number of 75 IU Vials	2625.0/ 35	2770.4/ 37	2463.3/ 33
Mean Treatment exposure [days] (SD)*	9.6 (1.4)	9.9 (1.3)	9.4 (1.4)

*SD – Standard deviation

Reviewer's comments:

1. **This study was not powered to show pregnancy (and the difference in clinical pregnancies was not statistically significant). The reviewer notes that other undetermined factors in this small population (such as antral follicle count) may have affected the treatment response and therefore, endpoints such as total oocytes and pregnancy outcomes.**
2. **This reviewer notes that the treatment exposure in Study 2000-02 appears to be less (by 2 treatment days) in this study as compared to MFK/IVF/0399E. The reason for this decreased duration in patients in study 2000-02 (compared to MFK/IVF/0399E) is unknown, although it is noted that the total number of vials (ampules) is greater in study 2000-02.**

In this reviewer's opinion, this potentially reflects a difference in the gonadotropin stimulation protocols in the United States compared to Europe.

3. **Study 2000-02 had a large proportion of recruited patients were over age 35 (approximately 30%).This is acceptable given that over 50% of ART procedures in the United States occur in patients over 35 years old.**

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

VII. Integrated Review of Safety

A. Brief statement of conclusions

The safety profile for the new Menopur® formulation (menotropins) is obtained from studies MFK/IVF/0399E, 2000-02 and 2000-01 and appears to be similar to the safety profiles obtained in the original clinical studies for Repronex®. The serious adverse events with gonadotropin use (ovarian hyperstimulation syndrome and multiple births) for Menopur® appear to be equivalent to the approved Repronex® formulation, and additionally to a recombinant human follicle-stimulating hormone product.

B. Description of Patient Exposure

Patient exposure for the approved Repronex® product has been ongoing since 1999, and is adequate. The patient exposure for the new r-hFSH formulation was limited to the three clinical trials (A total of 575 patients exposed to the new r-hFSH formulation in the three clinical studies [MFK/IVF/0399E, 2000-02 and 2000-01] that were submitted). However, since the safety of the Menopur® formulation appears to be similar to the Repronex®, exposure is adequate.

C. Methods and Specific Findings of Safety Review

The safety profile for the Menopur® formulation administered subcutaneously and intramuscularly was based on safety data obtained from three supportive clinical studies (MFK/IVF/0399E, 2000-02 and 2000-01).

Reviewer's comments:

1. **The safety profile for the Menopur® was also compared to safety data obtained in a large ART study (21884) for a recent new r-hFSH product (NDA 21-765/ Serial No. 000). This comparison was performed as the studies are comparable in terms of numbers of ART patients and clinical study initiation dates (Study MFK/IVF/0399E was initiated May 1999, Study 21884 was initiated July 2000).**

Study MFK/IVF/0399E: Patients undergoing assisted reproductive technology (*in vitro* fertilization and intracytoplasmic injection):

Patient Disposition/Treatment: The evaluable group assessed for safety included 727 subjects who were enrolled and treated with at least one dose of gonadotropins. Adverse events were coded using the WHO Adverse Event Reaction Terminology Dictionary, and the severity of adverse events was graded by the Sponsor using a modified WHO criteria.

The clinical safety assessments of concern reported by the Sponsor included:

1. Overall adverse events
2. Serious adverse events
3. Ovarian hyperstimulation syndrome
4. Study termination rate
5. Multiple pregnancy/Total abortion rates/Ectopic rates
6. Other safety issues

1. Overall adverse events:

The overall adverse events were examined for all three treatments groups for study MFK/IVF/0399E. In the treated patient population, 414 patients (56%) reported adverse events with Menopur® compared to 204 patients (54% in the r-hFSH formulation group.

In each of the treatment groups, the number of patients with adverse events included:

- 210 patients (61.2%) in the Menopur® group
- 204 patients (64.6%) in the r-hFSH group

The most frequently reported adverse events in all treatment groups combined were headache and abdominal pain. Abdominal pain and headaches have been noted to occur with use of the other gonadotropins (See NDA 21-765).

a. Headache was the second most common reported adverse event. The proportion of patients with headaches in the three treatment groups included:

   - 98 reported patients (26.3%) in the Menopur® group
   - 82 reported patients (23.2%) in the r-hFSH group

b. Abdominal pain was the most common reported adverse event.

   - 59 reported patients (15.8%) in the Menopur® group
   - 59 reported patients (16.7%) in the r-hFSH group

Reviewer's comments:

- **The overall rates of adverse events in the Menopur® formulation group were similar to rates seen in the r-hFSH treatment group and the adverse event rates seen in a similar recent study of r-hFSH [NDA 21-765/N-000/study 21884]. (See Appendix 3 – Table 1A).**
- **There was an increased number of patients with abdominal pain reported in the Menopur® group than the r-hFSH groups. In this reviewer's opinion, it is unknown whether this increased reporting of abdominal pain is related to the actual oocyte retrieval process (differences in anesthesia, differences in retrieval procedures), or directly related to the Menopur® formulation.**

- **The rates of headaches in the Menopur® group (26.3%) was higher than seen in the r-hFSH group (23.2%) and higher than in a comparable study (21884) with a comparable r-hFSH formulation (18.6%) (See Appendix 3 – Table 2A). It is somewhat reassuring to note that the rate of migraines was less than 2% (6 patients [1.6%] in the Menopur® group compared to 1 patient [0.3%] in the r-hFSH group. In addition, it is important to note that other concomitant medications used during this study (MFK/IVF/0399E) could have increased the rate of headaches observed, and therefore, confound whether Menopur® formulation is responsible for the headaches. These medications include: anesthesia for oocyte retrieval, pain medication given for oocyte retrieval, luteal phase support, and gonadotropin agonist treatments.**

In this reviewer's opinion, the label should reflect the rate of headaches noted in study MFK/IVF/0399E.

2. Serious adverse events:

There were no deaths seen in study MFK/IVF/0399E. Thirty-two patients (4.4%) had serious adverse events were reported:

- The Menopur® SC formulation group: 6 ectopic pregnancies, 5 ovarian hyperstimulation syndrome [OHSS] (including one patient that developed a deep vein thrombosis after the diagnosis of OHSS), 3 missed abortions, 2 threatened abortions, 1 gastritis, 1 patient hospitalized with abdominal pain and vaginal bleeding 2 weeks post-transfer and 1 hyperemesis gravidarum.
- The r-hFSH group: 4 ovarian hyperstimulation syndrome, 2 ectopic pregnancies, 3 miscarriages, 2 missed abortions, 1 patient hospitalized with abdominal pain 2 weeks post-transfer, 1 patient with anaphylaxis.
- Prior to the start of gonadotropins: 1 patient developed a suspected ectopic pregnancy and ultrasound detected a new endometrial polyp in one patient.

Reviewer's comments:

- **The overall serious adverse event rates appear to be roughly equivalent when comparing the two gonadotropin treatment groups (Menopur® SC group and r-hFSH group).In this reviewer's opinion, the most concerning adverse event was in a patient (265-010) treated with Menopur® SC who had a deep vein thrombosis. This patient had been hospitalized for severe ovarian hyperstimulation syndrome with a peak estradiol of 7,242 pg/mL and was pregnant with twins.**

However, deep venous thrombosis is a known complication of ovarian hyperstimulation syndrome[12] and the risk of thromboembolism also increases with concomitant pregnancy (especially multiple gestations). Therefore, although thromboembolic events are rare (less than 1% of patients hospitalized with moderate and severe OHSS)[12], the rate of this event was actually less than 1% of the Menopur® treatment group. It is reassuring that no other thromboembolic events were noted in this study.

- **The overall ectopic pregnancy and miscarriage rates were less than 2% in both treatment arms. Both ectopic pregnancies and miscarriages are well recognized complications associated gonadotropin use. In this reviewer's opinion, the safety profile for these events does not reveal new trends or additional safety concerns.**

3. Ovarian hyperstimulation syndrome:

The overall rate for ovarian hyperstimulation syndrome (OHSS) was reported as an adverse event in 47 patients. OHSS was reported in:

- 27 patients (7.2%) using the Menopur® SC group
- 20 patients (5.6%) in the r-hFSH group

Severe ovarian hyperstimulation was reported in 2 patients (0.5%) in the Menopur® SC group and one patient (0.3%) in the r-hFSH group.

Reviewer's comments:

- **The overall rate of OHSS (7.0%) in the Menopur® group was slightly higher than seen in the r-hFSH group (5.6%) or in a recent ART study [NDA 21-765 – Study 21884] of 4.6%. However, Study MFK/IVF/0399E was not powered to demonstrate a difference in OHSS rates, and the difference in overall OHSS does not appear to be clinically significant.**
- **Additionally, one patient in the Menopur® group with OHSS (Subject #222009) was listed as having moderate OHSS, although her peak estradiol level was 9,507 pg/mL. Estradiol levels over 6,000 pg/mL have been associated with a more severe form of OHSS[13]. However, reclassifying this case as severe (0.8%) does not significantly alter the rate of severe OHSS for Menopur® in this study.**

This reviewer notes that moderate to severe OHSS occurred in 9 patients (2.4%) in the Menopur® group, almost twice than the rate seen in the r-hFSH group (3 patients - 1.1%). It is unknown whether the rate of OHSS (both overall and severe) reflects practice patterns in European centers, or is a rate that will be comparable to use of Menopur® in the US. However, in this reviewer's opinion, there is limited evidence to suggest that use of Menopur® SC may generate an increased number of OHSS cases as compared to an r-hFSH only product.

4. Study termination for study MFK/IVF/0399E:

Treatment with the gonadotropins (the Menopur® formulation or the r-hFSH formulation) or human chorionic gonadotropin (hCG) was withheld for any of the following reasons (i.e. study termination):

- Any deterioration in the patient's physical condition
- Poor patient cooperation or compliance
- Intake of drugs not allowed in the study
- New diseases that influence the effectiveness of the trial medication
- Intolerable adverse events
- Occurrence of administrative reasons unrelated to the study

The major cancellation that results in a safety concern with gonadotropin use is cancellation of a treatment cycle because of an adverse event.

a. Patients that were cancelled for an adverse event included:

- Menopur® group:
  - 1 patient cancelled for gastritis (0.2%)
  - 9 patients cancelled for the risk of OHSS (2.4%)

- r-hFSH group:
  - 1 patient cancelled for anaphylaxis (0.3%)
  - 6 patients cancelled for the risk of OHSS (1.7%)

Reviewer's comment: No differences or trends in cycle cancellations for OHSS were noted across the two treatment groups.

5. Multiple pregnancy rate/Miscarriage/Ectopic Rate:

a. The multiple pregnancy rates in the two primary efficacy treatment groups. (See Appendix 2 – Table 8A).
   - 30 Multiple pregnancies (8%) in the Menopur® group
   - 28 Multiple pregnancies (8%) in the r-hFSH group

b. The total abortion rate was reported (See Appendix 2 – Table 8A):
   - 7 total abortions (1.9%) in the Menopur® group
   - 11 total abortions (3.1%) in the r-hFSH group

c. The ectopic pregnancy rate was reported (See Appendix 2 – Table 8A):
   - 6 ectopic pregnancies (1.6%) in the Menopur® formulation group
   - 2 ectopic pregnancies (0.6%) in the r-hFSH group

Reviewer's comments:

1. **The multiple pregnancy rate for the Menopur® group was similar to the rate seen in the r-hFSH group (See Appendix 2 - Table 8A). However, it is difficult to compare this rate since no follow-up multiple birth information was included in this submission. However, this information would not be useful as this reviewer has concerns that the treatment of multiple births (and use of fetal reduction) may not be translatable from Europe to centers in the United States.**
2. **The numbers of miscarriages and ectopic pregnancies were compared between the two treatment groups. The difference between the miscarriage and ectopic rates were not clinically different between treatment groups.**
3. **It is also important to note that study MFK/IVF/0399E was not powered to demonstrate clinical differences between any of these secondary endpoints.**

6. Other issues related to safety:
   - The Sponsor reported that laboratory data (blood chemistry, hematology, and hormonal data) could be historical (≤ 12 months old).
   - The Sponsor reported that local tolerance was similar in both treatment groups (inflammation at injection site in 4.8% in the Menopur® group compared to 3.4% in the r-hFSH group and pain at injection site in 4.6% in the Menopur® group compared to 3.7% in the r-hFSH group)

Reviewer's comments:

1. **No hematology, chemistry, liver function data was collected immediately pre- or post-study. In this reviewer's opinion, the safety profile for Menopur® would have benefited from obtaining this additional laboratory data.**
2. **In this reviewer's opinion, it is not possible to assess local tolerance in an open-label study. Therefore, [redacted] would need to be derived from additional clinical studies that specifically evaluated injection site reactions.**

Study 2000-02: Patients undergoing In Vitro Fertilization (IVF)

Patient disposition/treatment: The evaluable group assessed for safety included 190 subjects who were enrolled and had at least one injection of study medication. Adverse events were coded using the WHO Adverse Event Reaction Terminology Dictionary.

The severity of adverse events was graded by the Sponsor using modified WHO criteria. The modified WHO criteria for severity of adverse events were graded using a four point scale (mild, moderate, severe and life-threatening).

The safety assessments reported by the Sponsor included:

1. Overall adverse events
2. Serious adverse events
3. Ovarian hyperstimulation syndrome
4. Study termination rate
5. Multiple pregnancy/Total abortion rates/Ectopic rates
6. Other issues related to safety:

1. Overall adverse events:

The overall adverse events were examined for the three treatment groups in all three treatment cycles. In the treated patient population, (patients treated with at least one dose of gonadotropin), 137 of 190 total treated patients (72.1%) reported at least one adverse event during the study (see Appendix 3 - Table 1B).

In each of the treatment groups, the number of patients with adverse events included:

- 41 patients (67.2%) in the Menopur® SC group
- 47 patients (72.3%) in the Menopur® IM group
- 48 patients (75.0%) in the Repronex® SC group

The most frequently reported adverse event in all treatment groups combined were abdominal cramps (21.0%) and headache (20%). The most common adverse event was injection site reactions (33.7%). Abdominal cramps and headaches have been noted to occur with use of the approved Repronex® formulation (See NDA 21-047).

a. Abdominal cramps were the most common reported adverse event.

- 13 patients (21.3%) in the Menopur® SC group
- 13 patients (20.0%) in the Menopur® IM group
- 14 patients (21.9%) in the Repronex® SC group.

b. Headache was the second most common reported adverse event. The proportion of patients with headaches in the three treatment groups included:

- 13 patients (21.3%) in the Menopur® SC group
- 12 patients (18.5%) in the Menopur® IM group
- 13 patients (20.3%) in the Repronex® SC group

c. Injection site reactions were the third most common reported adverse event. The proportion of patients with headaches in the three treatment groups included:

- 7 patients (11.5%) in the Menopur® SC group
- 12 patients (18.5%) in the Menopur® IM group
- 14 patients (21.9%) in the Repronex® SC group

Reviewer's comments:

1. **The rate of abdominal cramps is equivalent between treatment groups, although if this overlaps abdominal pain complaints are unknown. In this reviewer's opinion, the abdominal cramps are related to the ART procedures rather than the gonadotropin used.**
2. **Headaches were less common in this IVF study (2000-02) than in the MFK/IVF/0399E study (Appendix 3 – Table 1A), although similar to a recent study of r-hFSH (See NDA 21-765/N-000/study 21884 [See Appendix – Table 1A). The rate of headaches in the r-hFSH treatment is similar compared to the two Menopur® groups.**

   The actual headache rate with Menopur® use is difficult to assess as other factors may result in headaches. These factors include the gonadotropin-releasing hormone agonist selected and other concomitant medications used for IVF (such as anesthesia). In addition, baseline headache rates in were not evaluated, so it is difficult to draw any conclusions.
3. **Injection site reactions appeared to be decreased in the Menopur® groups. However, if the Sponsor wishes to pursue [ ] additional studies would be necessary.**
4. **Other adverse events, including breast pain, nausea and vaginal hemorrhage were lower for Menopur® SC group compared to Menopur® IM or Repronex® groups. (See Appendix 3 – Table 1B). In contrast, Menopur® SC and IM had a lower rate of injection site reactions (4.9% and 4.6%) compared to the Repronex® group (34.4%).**

In this reviewer's opinion, this small study population does not provide substantial evidence that Menopur® alters adverse events compared to other approved gonadotropins. If the Sponsor wishes [ ] separate clinical studies would be required.

2. Serious adverse events:

There were no deaths or thromboembolic events in study 2000-02. There were 7 total serious adverse events reported (7.8%) for study 2000-02 including:

- The Menopur® SC group: 1 patient with OHSS
- The Menopur® IM group: 2 patients with OHSS
- The Repronex® SC group: 1 patient with dehydration, one with OHSS, one right ovarian rupture with hemothorax and one patient with a pelvic abscess

Reviewer's comments: The serious adverse event rate appears to be roughly equivalent between the three gonadotropin treatment groups. The serious adverse event data in study 2000-02 does not demonstrate new trends or additional safety concerns. Of note, the incidence of pelvic abscess and ovarian rupture after transvaginal oocyte retrieval is rare (0.2%), but has been reported and are probably related to the ART retrieval procedure and not the gonadotropin used[14,15]. It is also important to note that neither of these complications occurred in the Menopur® group. For this reason, and the rarity of these complications, this reviewer recommends that the Sponsor continue to monitor these complications in the post-marketing period.

3. Ovarian hyperstimulation syndrome:

The overall rate for ovarian hyperstimulation syndrome was reported as an adverse event in 7 patients. Ovarian hyperstimulation was reported by treatment group in:

- 1 patients (1.6%) using the Menopur® SC formulation
- 4 patients (6.2%) in the Menopur® IM formulation
- 2 patients (3.1%)in the Repronex® SC group

Severe ovarian hyperstimulation was reported in two patients (0.4%), one in each of the Menopur® groups, and none in the Repronex® group.

Reviewer's comments:

- **The overall rate of OHSS in the Menopur® SC group is similar to the rate seen with the approved Repronex® group.**
- **The overall rate of ovarian hyperstimulation in the Menopur® IM group is somewhat higher than the approved Repronex® product. However, this rate is almost identical to the rate seen with Repronex® SC in the EU study (MFK/IVF/0399E) of 7.2%.**
- **Only one patient (#01-008 at center 013) with OHSS had a peak estradiol level of over 6,000 pg/mL. This patient was in the Repronex® SC group and was not considered a severe OHSS case by**

the investigator. In this reviewer's opinion, this patient's estradiol and treatment with intravenous albumin, she should have been classified as severe on the basis of an elevated estradiol level and requiring a significant therapeutic intervention[13]. However, even if this patient is reclassified as severe, the overall and severe ovarian hyperstimulation syndrome for Repronex® SC do not appear to be clinically different from the approved Repronex® group.

4. Study termination:

The Sponsor stated that reasons for study termination of the treatment cycle: (i.e. withholding gonadotropin therapy (Menopur® SC, Menopur® IM formulation or the approved Repronex® SC) or human chorionic gonadotropin (hCG) therapy. The reasons the Sponsor listed for possible study termination included:

- Death
- Drug-related adverse event
- Physician instigated withdrawal
- Insufficient compliance with protocol treatments and/or evaluations
- Non-drug related reasons
- Reasons unknown (i.e. patient lost to follow-up)
- Patient choice

The major cancellation that results in a safety concern with gonadotropin use is the cancellation of a treatment cycle because of an adverse event. The Sponsor reported:

1. No patients in the Menopur® SC group were cancelled for the risk of ovarian hyperstimulation.
2. One patient chose not to have an embryo transfer after developing moderate OHSS.
3. One patient was lost-to-follow-up after embryo transfer.

Reviewer's comment: One patient (1.5%) cancelled her cycle to prevent more severe adverse event (OHSS) from developing. In this reviewer's opinion, the fact that only one patient in this study was cancelled for an adverse event reflects the small population studied in study 2000-02, not superiority of Menopur® IM. No other patient had their cycles cancelled because of an adverse event, although one patient had oocyte retrieval and embryo transfer and was lost to follow-up.

5. Multiple birth/spontaneous abortion/ectopic pregnancy rate:
   a. The multiple birth rates of the primary efficacy treatment groups includes (See Appendix 2 – Table 7B):

      - 7 patients had twin pregnancies in the Menopur® SC group.
      - 8 patients had twin pregnancies and 2 had triplet pregnancies in the Menopur® IM group.

- 7 patients had twin pregnancies and one had a triplet pregnancy in the Repronex® SC group.

b. The spontaneous abortions reported (See Appendix 2 – Table 7B):
   - 1 abortions (1.6%) in the Menopur® SC group
   - 1 abortions (1.5%) in the Menopur® IM group
   - 0 abortions (0%) in the Repronex® SC group

c. The ectopic pregnancy rate was reported (See Appendix 2 – Table 7B):
   - 0 patient (0%) in the Menopur® SC group
   - 0 patients (0%) in the Menopur® IM group
   - 1 patient (1.6 %) in the Repronex® SC group

Reviewer's comments:

1. **The multiple pregnancy rates for the two Menopur® groups are not clinically different from the approved Repronex® group (See Appendix 2 – Table 7B). In addition, the 11-15% multiple birth rate seen in the Menopur® groups in study 2000-02 is consistent with previous multiple birth rates reported with ART of 12-35% [7,16].**
2. **The rates of miscarriage and ectopic pregnancy rates are not clinically different with use of the Menopur® formulation either subcutaneously or intramuscularly. However, it is important to note that study 2000-02 was not powered to detect clinical differences in these secondary endpoints.**

6. Vital signs/Laboratory findings/Other issues related to safety:

   - No deaths occurred in the study.
   - The Sponsor reported that there were no significant laboratory abnormalities post-treatment.
   - Although vital signs were not recorded pre- or post-treatment, only two adverse events related to postural hypotension were recorded.

Reviewer's comments:

1. **As a group, gonadotropins have not been demonstrated to cause significant hematology, chemistry, liver function or vital sign abnormalities. However, in this reviewer's opinion, the safety analyses for Menopur® would have benefited from recording post-treatment clinical laboratory data in this US ART study.**
2. **In this reviewer's opinion, it is not possible to assess local tolerance in an open-label study. Therefore, [redacted] would need to be derived from additional clinical studies that specifically evaluated injection site reactions.**

Study 2000-01: Patients undergoing Ovulation Induction (OI)

Patient disposition/treatment: The evaluable group assessed for safety included 120 subjects who were enrolled and had at least one injection of study medication. Adverse events were coded using the WHO Adverse Event Reaction Terminology Dictionary.

The severity of adverse events was graded by the Sponsor using modified WHO criteria. The modified WHO criteria for severity of adverse events were graded using a four point scale (mild, moderate, severe and life-threatening).

The safety assessments reported by the Sponsor included:

1. Overall adverse events
2. Serious adverse events
3. Ovarian hyperstimulation syndrome
4. Study termination rate
5. Abortion rates and ectopic rates
6. Vital signs/Laboratory findings/Other issues related to safety

1. Overall adverse events:

The overall adverse events were examined in the treated patient population, (patients treated with at least one dose of gonadotropin), 79 total treated patients (65.8%) reported at least one adverse event during the study (see Appendix 3 - Table 1C).

In each of the treatment groups, the number of patients with adverse events included:

- 25 patients (67.6%) in the Menopur® SC group
- 21 patients (53.8%) in the Menopur® IM group
- 33 patients (75%) in the Repronex® SC group

The most frequently reported adverse event in all treatment groups combined were injection site reactions (16.7%), headache (15.8%), and abdominal pain (13.3%).Injection site reactions, abdominal pain and headaches have been noted to occur with use of the approved Repronex® formulation (See NDA 21-047).

a. Headache was a common adverse event. The proportion of patients with headaches in the three treatment groups included:

   - 5 patients (13.5%) in the Menopur® SC group
   - 7 patients (17.9%) in the Menopur® IM group
   - 7 patients (15.9%) in the Repronex® SC group

b. Injection site reactions were the second most common reported adverse event

- 5 patients (13.5%) in the Menopur® SC group
- 4 patients (10.3%) in the Menopur® IM group
- 11 patients (25%) in the Repronex® SC group.

c. Abdominal pain was the third common reported adverse event

- 3 patients (8.1%) in the Menopur® SC group
- 4 patients (10.3%) in the Menopur® IM group
- 9 patients (20.5%) in the Repronex® SC group.

Reviewer's comments:

- **Headaches were less common in the Menopur® SC group in this ovulation induction (OI) study [13.5%] (Appendix 3 – Table 1C) than the 2000-02 ART study [21.3%] (Appendix 3 – Table 1A). In this reviewer's opinion, the decrease in headaches between studies reflects the shorter dose and duration of treatment in this OI study compared to the IVF study (2000-02). Of some concern is that the headache rate of Menopur® SC group was more common than a previously completed OI study using the approved Repronex® SC (5.6%)[17]. However, the rate of headaches in the Menopur® SC treatment is similar when compared to the other two treatment groups (i.e. the Menopur® IM and Repronex®) in study 2000-01. In this reviewer's opinion, the reason for the significant number of headaches seen with use of gonadotropins in study 2000-01 is unknown, but can be related to a multitude of factors including baseline headache rates, length of treatment and concomitant medications.**
- **A second adverse event of concern with gonadotropin use is abdominal pain. The Sponsor separated abdominal pain from cramps (although in this reviewer's opinion, the distinction between these symptoms may not be clear). Moderate to severe abdominal pain or cramps was seen in:**
  - **3 patients (8.1%) in the Menopur® SC group**
  - **3 patients (7.7%) in the Menopur® IM group**
  - **6 patients (13.6%) in the Repronex® SC group**

  It is unknown why the approved Repronex® SC group had an increased patient number with moderate to severe abdominal pain or cramps. In this reviewer's opinion, this may reflect decreased potency of Menopur®.
- **Although injection site reactions appeared to be clinically lower in the two Menopur® groups, a separate study would be required to look at local tolerance**

- **Other adverse events, including breast pain and vaginal hemorrhage for the Menopur® groups were not significantly different from rates in the Repronex® group. (see Appendix 3 – Table 1C).**

2. Serious adverse events:

There were no deaths or thromboembolic events in study 2000-01. There was only one serious adverse events reported (%) for study 2000-01:

- The Menopur® SC group: One patient with OHSS
- No serious adverse events were reported in either the Menopur® IM group or the approved Repronex® group.

Reviewer's comment: The serious adverse event rate appears to be roughly equivalent between the three gonadotropin treatment groups. The serious adverse event data in study 2000-01 does not demonstrate new trends or additional safety concerns.

3. Ovarian hyperstimulation syndrome:

The overall rate for ovarian hyperstimulation syndrome was reported as an adverse event in 6.5% of patients in this study. Ovarian hyperstimulation was reported by treatment group in:

- 8 patients (21.3%) using the Menopur® SC group
- 2 patients (5.1%) in the Menopur® IM
- 4 patients (9.1%) in the Repronex® SC group

Severe ovarian hyperstimulation was reported in one patient (2.7%) in the Menopur® SC group. No cases of severe ovarian hyperstimulation were reported in the Menopur® IM or Repronex® SC groups.

Reviewer's comments: The overall rate of ovarian hyperstimulation syndrome (OHSS) of 21% (8 patients) for the Menopur® SC is higher than the rates seen in the other Menopur® IM or Repronex® SC groups. In addition, the overall rate of ovarian hyperstimulation for Menopur® SC is significantly higher than a previous published OHSS rate for patient undergoing ovulation induction with Repronex® SC (8.3%)[17]. However, this reviewer notes that 50% of the cases of OHSS reported in this small study (4 patients) had mild OHSS. More important in evaluating ovarian hyperstimulation is the rate of severe OHSS. The rate of severe OHSS seen in the Menopur® SC group (2.7% of the Menopur® SC patients treated) is equivalent to the 2.7% rate seen in a small published ovulation induction study for the approved Repronex® SC product[17], although higher than a recent ovulation induction study for an approved r-hFSH formulation (0%) (See NDA 21-765/N-000).

In this reviewer's opinion, since this OI study was not powered to show a difference in the rate of OHSS between groups, it is unknown whether the higher rates of overall and severe OHSS seen in the Menopur® SC group are clinically significant, or different from r-hFSH products.

- **It is noted that one patient had an estradiol level of over 6,000 pg/mL (patient #08-007/Center 009). This patient was classified as having moderate OHSS. In this reviewer's opinion, although she had an estradiol level that would meet the criteria for severe OHSS, this patient avoided severe OHSS by not receiving hCG.**

4. Study termination:

The Sponsor stated that reasons for study termination of the treatment cycle: (i.e. withholding gonadotropin therapy [Menopur® SC, Menopur® IM or Repronex® SC) or human chorionic gonadotropin (hCG) therapy included:

- Death
- Drug-related adverse event
- Physician instigated withdrawal
- Insufficient compliance with protocol treatment and/or evaluations
- Non-drug related reason
- Reason unknown (i.e. patient lost to follow-up)
- Patient's choice

The major cancellation that results in a safety concern with gonadotropin use is the cancellation of a treatment cycle because of an adverse event.

a. Patients that were cancelled for an adverse event (ovarian hyperstimulation risk included:

- 2 patients (5.4%) of 37 total patients in the Menopur® SC group
- 0 patients (0%) of 39 total patients in the Menopur® IM group
- 2 patients (4.5%) of 44 total patients in the Repronex® SC group

Reviewer's comments:

1. **This reviewer notes that although death is listed as a potential side effect of menotropins (including Menopur® and Repronex®), no deaths have been reported in any of the submitted clinical studies.**
2. **The rate of cycle cancellation for the risk of ovarian hyperstimulation appeared to be clinically lower for the Menopur® IM group than the other two treatment groups, however this study was not powered to demonstrate differences in OHSS rates. This reviewer notes that 2 patients (one in the Menopur® SC group and one in the Repronex® SC group) were cancelled for the risk of OHSS.**

However, in this reviewer's opinion, there does not appear to be a significant difference in the rate (or risk) of ovarian hyperstimulation between Menopur® SC and Repronex® SC. This reviewer also notes that although Menopur® IM appears to have a better profile of OHSS, this is probably a reflection of the small numbers in the study, not an improved safety profile.

5. Multiple birth/miscarriage/ectopic pregnancy rate:

   a. The multiple birth rates of the primary efficacy treatment groups includes: (See Appendix 2 – Table 8C).

      - 1 patients had twin birth in the Menopur® SC group.
      - 2 patients had twin births and one had a triplet birth in the Menopur® IM group.
      - 5 patients had twin births in the Repronex® SC group.

   a. The spontaneous abortion rate was reported (See Appendix 2 – Table 8C):
      - No patients were noted to have spontaneous abortions in any of the three treatment groups (Menopur® SC, Menopur® IM or Repronex® SC.

   b. The ectopic pregnancy rate was reported (See Appendix 2 – Table 8C):
      - 0 patient (0%) in the Menopur® SC group
      - 0 patients (0%) in the Menopur® IM group
      - 1 patient (2.3%) in the Repronex SC group

6. Other safety issues:

   - No deaths occurred during this study.
   - Routine clinical laboratories were not assessed in this study.
   - No clinically significant differences were noted in mean change from baseline to exit in vital signs (including blood pressure and heart rate).

Reviewer's comments:

1. **The rate of multiple births, spontaneous abortions and ectopic pregnancies in the two Menopur® groups is not clinically different from that seen in the Repronex® SC group. However, the abortion rate in the Menopur® group is much lower than data from a previous ovulation induction trial (See Study 5727 (NDA 20-378) – reported as having a miscarriage rate of 22.7% in the recombinant follitropin alfa treatment group).**

2. **In this reviewer's opinion, this study had an inadequate patient population to evaluate the multiple birth and/or spontaneous abortion rates seen does not represent superiority of Menopur®, but that this OI study is under-powered to demonstrate significant differences in overall miscarriage or ectopic pregnancy rates.**
3. **In this reviewer's opinion, there is insufficient data to determine whether there will be changes in clinical laboratories with this new Menopur® formulation. However, as the Sponsor notes, there have not been indications that any of the urinary menotropins directly alter any clinical laboratory parameter, and there is no indication that any trends in abnormal clinical laboratory data were seen in the adverse event data. The reviewer recommends that the Sponsor continue to collect data on any reports of abnormal clinical laboratory data for future evaluation.**
4. **In this reviewer's opinion, it is not possible to assess local tolerance in an open-label study. Therefore, [ ] would need to be derived from additional clinical studies [ ]**

D. Adequacy of Safety Testing

Safety data has been collected for the approved Repronex® (the initial approved urinary menotropin from the Sponsor) formulation since the NDA (21-047) since it was initially submitted in 1998 and through subsequent annual reports. Patient exposure has been adequately documented from a safety perspective for the approved Repronex® formulation. The safety of the new Menopur® formulation is based on documentation of clinical non-inferiority to the approved Repronex® or follitropin alfa product for each indication. This is acceptable, especially in light of the similar safety profiles to Repronex®, although the actual numeric data is very limited.

E. Summary of Critical Safety Findings and Limitations of Data

The current adverse event data for the Menopur® formulation for studies MFK/IVF/0399E, 2000-02 and 2000-01 are included in NDA 21-663 (submitted December 29, 2003). No deaths were reported by the Sponsor during the three clinical studies (MFK/IVF/0399E, 2000-02 and 2000-01). The reported adverse event profile for the Menopur® formulation (administered subcutaneously or intramuscularly) is not significantly differ from the safety profile seen in the approved Repronex® treatment arm. Furthermore, the safety profile of the Menopur® formulation (administered subcutaneously) is not significantly different from a recombinant reference gonadotropin product (follitropin alfa). The Sponsor reports no new trends or safety issues have been demonstrated in the adverse event profile of the Menopur® formulation administered subcutaneously or intramuscularly.

VIII. Dosing, Regimen, and Administration Issues

The dosing regimens presented in the three clinical studies (MFK/IVF/0399E, 2000-02 and 2000-01) are similar to the proposed dosing regimens for the proposed indications in the label for the Menopur® formulation. Referring to the proposed dosing regimen for ART, the proposed label for Menopur® states that the maximum recommended dose is 450 IU and the maximum duration of treatment is 20 days (identical to the dosing regimen used in study MFK/IVF/0399E). [

]

Reviewer's comments:

1. **For the ART studies it would have been optimal if both studies MFK/IVF/0399E (European ART study) and 2000-02 (US IVF study) used the exact same treatment regimen. However, in this reviewer's opinion, study MFK/IVF/0399E is a more comprehensive study. Therefore, the dosage regimen recommended from study MFK/IVF/0399E is acceptable for the proposed label.**
2. [

]
3. **This reviewer recommends that the Sponsor use similar language for termination of treatment for [ ] ART indications. The label should state that "If any serious medical condition occurs, including a significant risk for developing moderate to severe OHSS, then treatment with Menopur® may be discontinued and/or administration of hCG should be withheld.**
4. **This reviewer also notes that the label states [ ] [ ] could be used for down-regulation. Since none of the clinical studies used [ ] this reviewer recommends removal of language regarding the use of [ ] until the Sponsor submits additional clinical studies to support the use of these agents with Menopur®.**

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The Menopur® formulation is being considered for conditions that occur only in women.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Clinical studies of the Menopur® formulation did not include patients aged 65 and over. Use of the Menopur® formulation is contraindicated in pregnancy. The three supportive clinical studies (MFK/IVF/0399E, 2000-02 and 2000-01) did not include geriatric or pregnant patients. However, it is not anticipated that the new Menopur® formulation would be used in geriatric or pregnant patient populations. The data presented by the Sponsor is too limited to make any definitive conclusions whether race or ethnicity would make create differences in the safety or efficacy of the new Menopur® formulation (r-hFSH).

C. Evaluation of Pediatric Program

Menopur® is not indicated for use in pediatric populations and safety and efficacy in such patients have not been established. It is not anticipated that the new Menopur® formulation would be used in a pediatric population given the current proposed indications.

X. Conclusions and Recommendations

A. Conclusions

- This reviewer recommends an approvable action for the new Menopur® formulation administered subcutaneously for the proposed indication of follicular development and pregnancy in ovulatory female patients undergoing assisted reproductive technology (ART) based on one clinical study presented (MFK/IVF/0399E). Analysis of the data show that subcutaneously administered Menopur® demonstrate non-inferiority of the primary efficacy endpoint of clinical pregnancy to an approved comparator for ovulatory patients undergoing assisted reproductive technology procedures.

- This reviewer recommends a not approvable action for the new Menopur® formulation administered intramuscularly for the proposed indication of follicular development and pregnancy in ovulatory female patients undergoing assisted reproductive technology (ART) based on one clinical study presented (2000-02). Analysis of the data show that intramuscularly administered Menopur® demonstrate non-inferiority of the primary efficacy endpoint of clinical pregnancy to an approved comparator for ovulatory patients undergoing assisted reproductive technology procedures.

The reviewer recommends

B. Recommendations

If the Sponsor wishes to seek approval for the current Menopur formulation, the Sponsor should conduct a new two new studies to demonstrate the efficacy of Menopur®. One clinical study should demonstrate the non-inferiority of intramuscular administration of Menopur® for ovulatory patients undergoing multiple follicular development and pregnancy in patients undergoing assisted reproductive technology procedures to an approved drug product.

. Ideally, these studies should be a double-blinded, double-dummy comparative studies using an approved active comparator with an endpoint of clinical pregnancy to demonstrate that Menopur® is both clinically and statistically non-inferior to the active comparator for the proposed indications.

Appendix 1

A. Overview of Completed Original Comparative Clinical Trials for NDA 21-047 using the approved Repronex® formulation.

1. Study 97-01 – An open-label, randomized, parallel-group, multi-center ovulation induction study in the United States that included 115 infertile women after pituitary down-regulation with a gonadotropin-releasing hormone agonist (leuprolide acetate).
   - Primary endpoint was the number and percentage of patients who ovulated.
   - The number of patients that ovulated with Repronex® was 23 of 26 patients intramuscularly (63.9%) compared to 25 of 36 patients (69.4%) receiving Repronex® subcutaneously and 21 of 36 patients (58.3%) receiving Pergonal® (USP menotropins) intrmuscularly. There were no statistically or clinically significant differences between the three treatment groups.

2. Study 97-02 – An open label, randomized, parallel-group, multi-center IVF-ET study in the United States that included 186 infertile women after pituitary down-regulation with a gonadotropin-releasing hormone agonist.
   - Primary endpoint was the number of oocytes retrieved per cycle.
   - The mean number of oocytes retrieved for Repronex® administered intramuscularly was 13.6 (± 7.7) in 65 patients compared to 12.7 (± 7.8) oocytes in 60 patients receiving Repronex® subcutaneously and 13.6 (± 7.8) in 61 patients receiving Pergonal® intramuscularly. There were no statistically or clinically significant differences between the three treatment groups.

3. Study 96-01NL – An open label, uncontrolled IVF-ET study in Europe that included 100 infertile women after pituitary down-regulation with a gonadotropin-releasing hormone agonist to assess the efficacy and safety for one cycle of IVF treatment. This study provided additional safety data for the approved Repronex® product delivered subcutaneously.

Appendix 1

B. References:

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Appendix 1

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Appendix 1

C. Principal investigator list for study MFK/IVF/0399E

Center Number	City, Country	Principal Investigator
11	Brussels, Belgium	Paul Devroey
21	Lubeck, Germany	Klaus Diedrich
22	Augsburg, Germany	Klaus-Friedrich Hiller
23	Hamburg, Germany	Klaus Rudolph
24	Ulm, Germany	Karl Sterzik
25	Bonn, Germany	Han Van de Ven
26	Dusseldorf, Germany	Hugo Verhoeven
31	Haifa, Israel	Martha Dirnfeld
32	Tel-Hasomer, Israel	Jehoshua Dor
33	Zerifin, Israel	Raphael Ron-el
34	Jerusalem, Israel	Neri Laufer
35	Tel-Aviv, Israel	David Levran
36	Afula, Israel	Eliezer Shalev
41	Voorburg, Netherlands	Cornelis Jansen
42	Arnhem, Netherlands	Alexander Schmoutziguer
51†	Lausanne, Switzerland	M. Germound
52	Basel, Switzerland	Michael Haeberle
61	Liverpool, UK	J. Hewitt
62	London, UK	Mark Johnson
63	Cardiff, UK	Lukas Klentzeris
64	Newcastle, UK	Alison Murdoch
65	Romford, UK	Satha Sathanandan
66	Bath, UK	N. Sharp

† Did not enroll patients in this study

Appendix 1

Principal investigator list for study 2000-02:

Center Number	City, State	Principal Investigator
1*	Charlotte, NC	Jack Crain, MD
2	Greenville, SC	John Nichols, MD
3*	San Diego, CA	Michael Kettel, MD
4*	Valencia, CA	Sam Najmabadi, MD Brian Acacio, MD
5*	Tampa, FL	Timothy Yeko, MD
6*	Abington, PA	Stephen Somkuti, MD
7	Mount Pleasant, SC,	Grant Patton, MD
8*	Baton Rouge, LA	Bobby Webster, MD
9*	New Orleans	Richard Dickey, MD
10*	Philadelphia, PA	Benjamin Gocial, MD
11*	Indianapolis, IN	Leo Bonaventura, MD
12	Colorado Springs, CO	Paul Magarelli, MD
13*	Birmingham, AL	Michael Steinkampf, MD
14*	Aurora, CO	William Schlaff, MD Marcelle Cedars, MD
15	Seattle, WA	Michael Soules, MD

* Also participated in trial 2000-01

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Appendix 2

Table 1A - Demographic characteristic distribution for the Intent-to-Treat (ITT) patients in study MFK/IVF/0399E

Characteristic	Menopur® group	r-hFSH group
Age (yrs)		
N	373	354
Mean (SD**)	30.8 (4.2)	30.8 (4.2)
BMI (kg/m^2)		
N	373	354
Mean (SD**)	23.2 (2.9)	23.1 (2.9)
Race, n%		
N	373	342
White	356 (95.4)	342 (96.6)
Black	2 (0.5)	2(0.6)
Asian	13 (3.5)	9 (2.5)
Other	2 (0.5)	1 (0.3)

** SD – Standard Deviation

Table 2A – Baseline characteristic distribution for study MFK/IVF/0399E for the Intent-to-Treat (ITT) population for the two treatment groups

Characteristic	Menopur® Group	r-hFSH group
Occurrence of the main causes of infertility		
N	373	354
Male Factor n(%)	251 (67.3)	233 (65.8)
Tubal Factor n(%)	64 (17.2)	60 (16.9)
Idiopathic n(%)	41 (11.0)	48 (13.6)
Endometriosis n(%)	9 (2.4)	8 (2.3)
Other n(%)	8 (2.1)	5 (1.4)
Previous Cycles of Infertility		
N	373	354
1	71 (47%)	66(42.9%)
2	47(31.1%)	49(31.8%)
3	33(21.9%)	39(25.3%)

** SD – Standard Deviation

Appendix 2

Table 3A – Other baseline characteristics related to treatment of the Intent-to-Treat (ITT) patients in study MFK/IVF/0399E

Treatment	Menopur® Group	r-hFSH group
GnRH downregulation		
Depot	250 (67%)	235 (66.4%)
Daily	123 (33%)	119 (33.6%)
IVF	120 (32.2%)	112 (31.6%)
ICSI	237 (63.5%)	221 (62.4%)
Mixed	2 (0.5%)	2 (0.5%)
Not done	14 (4%)	19 (5.4%)

** SD – Standard Deviation

Table 4A – Down-regulated serum estradiol levels for Intent-to-Treat (ITT) patients in study MFK/IVF/0399E

Serum Hormone	Menopur® Group	r-hFSH group
Total		
N	365	348
Mean E2 level* (SD**)	68.7 (52.1)	65.1 (39.2)
Median E2 level*	58	55.5
Range (pmol/L)	29 – 673	29-279
GnRH depot – IVF		
N	51	45
E2 level (SD)*	61.7 (29.4)	55.4 (33.5)
GnRH depot - ICSI		
N	188	170
E2 level (SD)*	65.3 (59.6)	61.1 (35.7)
GnRH daily – IVF		
N	67	66
E2 level (SD)*	81.9 (54.2)	81.4 (50.5)
GnRH daily – ICSI		
N	47	46
E2 level (SD)*	72.1 (32.3)	71.7 (36.5)

*E2 – serum estradiol levels in pmol/L
**SD – standard deviation

Appendix 2

Table 5A – Allocation of patients for Study MFK/IVF/0399E

Number of patients	Menopur®	r-hFSH
# Randomized	n=395	n=386
# Patient dropouts prior to start of gonadotropins	22 (5.6% of randomized)	32 (8.3% of randomized)
# Patients treated with at least one dose of gonadotropin (ITT)	373 (100%)	354 (100%)
#Treated with Depot GnRH	250	235
# Treated with Daily GnRH	123	119
# Patients with oocyte retrieval (% ITT)	361 (96.8%)	339 (95.8%)
#IVF/depot GnRH	52	45
#ICSI/depot GnRH	189	174
#IVF/daily GnRH	69	67
#ICSI/daily GnRH	49	47
Mixed/Other	2	6
# Patients with embryo transfer (% ITT)	336 (90.1%)	315 (89.0%)
#IVF/depot GnRH	49	41
#ICSI/depot GnRH	178	167
#IVF/daily GnRH	65	65
#ICSI/daily GnRH	47	45

Appendix 2

Table 6A – Key Protocol Violations in study MFK/IVF/0399E

Key Deviations	Menopur® (n=373)	r-hFSH (n=354)
Patient did not menstruate within the first two weeks of GnRH agonist treatment	14	4
Patient had an estradiol level > 200 pmol/L at 1st day of gonadotropin administration	7	3
Patient received the wrong medication (ongoing)	1	0
Patient's hCG administration was more than one day after last gonadotropin administration	47	44
IVF/ICSI – method performed differed from the method randomized to	4	8
Patient received Choragon® for luteal support	2	6

Appendix 2

Table 7A – Primary efficacy outcome table using clinical pregnancy rates for the ITT population in study MFK/IVF/0399E

Outcome	Menopur® group	r-hFSH group
Clinical Pregnancy Rate		
Sponsor's primary analysis		
All subjects		
Total n	373	354
Number of pregnancies (%)	87 (23.3%)	73 (20.6%)
Two sided 95% CI	*[-3.3, 8.7]*	
Division's primary analysis		
All subjects		
Total n	**374**	**353**
Number of pregnancies (%)	**90(24%)**	**72(20%)**
Two sided 95% CI	**[-2.4%, 9.7%]**	
Division's Modified ITT Analysis		
IVF subjects		
Total n	121	112
Number of pregnancies (%)	37 (30.5%)	22(19.8%)
95% CI	[-0.3%, 22%]	
ICSI subjects		
Total n	240	219
Number of pregnancies (%)	53(22.1%)	49(22.4%)
95% CI	[-7.9%,7.4%]	
Division's Modified ITT Analysis		
GnRHa* depot subjects		
Total n	247	232
Number of pregnancies (%)	56 (22.7%)	43(18.5%)
95% CI	[-3.1%, 11.4%]	
GnRHa* daily subjects		
Total n	114	112
Number of pregnancies (%)	31(27.2%)	27(24.1%)
95% CI	[-8.4%, 14.6%]	

*SD – Standard Deviation

* GnRHa - Gonadotropin-releasing hormone agonist.

Appendix 2

Table 8A - Pregnancy outcome for study MFK/IVF/0399E for the treated population

Outcome	Menopur® group	r-hFSH group
N	n=373	n=354
Clinical outcomes n (%)*		
Total Abortions†	7 (1.9)	11(3.1)
Ectopic	6 (1.6)	2 (0.6)
Livebirth	80 (21.4%)	67(18.7%)
	57	45
Singleton pregnancies	26	25
Twin pregnancies	4	3
Triplet pregnancies		

* Percentages are with respect to the total number of patients that received at least one dose of study medication (clinical outcome per attempt).
† Total abortions are defined as the total number of patients who had miscarriages and missed abortions.

Appendix 2

Table 1B - Demographic characteristic distribution for treated patients in study 2000-02

Characteristic	Menopur® SC	Menopur® IM	Repronex® SC
Age (yrs)			
N	61	65	64
Mean (SD*)	32.2 (3.7)	31.6 (3.5)	32.5 (4.1)
Weight (kg)			
N	61	65	64
Mean (SD*)	141 (24.4)	143(27.2)	141 (22)
BMI (kg/m^2)			
N	61	65	64
Mean (SD*)	24.4 (3.6)	24 (4)	24 (3.4)
Race, n (n%)			
N	61	65	64
White	47 (77%)	54 (83.1%)	54 (84.4%)
Black	7 (11.5%)	9 (13.8%)	1 (1.6%)
Asian	0	0	2 (3.1%)
Hispanic	5 (8.2%)	2 (3.1%)	5 (7.8%)
Other	2 (3.3%)	0	2 (3.1%)

* SD – Standard Deviation

Appendix 2

Table 2B – Other baseline characteristics for treated patients in study 2000-02

Characteristic	Menopur® SC	Menopur® IM	Repronex® SC
Total patients (N)	n=61	n=65	n=64
Occurrence of the main cause of infertility [n(n%)]			
Male Factor	5 (8.2%)	1 (1.5%)	3 (4.7%)
Tubal Factor	26 (42.6%)	34 (52.3%)	27 (42.2%)
Idiopathic	22 (36.1%)	20 (30.8%)	17 (26.6%)
Endometriosis	7 (11.5%)	8 (12.3%)	16 (25%)
Other	1 (1.6%)	2 (3.1%)	1 (1.6%)
Previous gonado-tropin cycles– [n (n%)]	41 (67.2%)	44 (67.7%)	43 (67.2%)
0	7 (11.5%)	4 (6.2%)	9 (14.1%)
1	1 (1.6%)	9 (13.8%)	2 (3.1%)
2	12 (19.7%)	8 (12.3%)	10 (15.6%)
>2			
Patients with previous full term births [n(n%)]			
0	61 (100%)	64 (98.5%)	63 (98.4%)
1	0	1 (1.5%)	1 (1.6%)
Patients with previous abortions [n(n%)]			
0	42 (68.9%)	43 (66.2%)	40 (62.5%)
1	16 (26.2%)	13 (20%)	13 (20.3%)
2	3 (4.9%)	4 (6.2%)	6 (9.4%)
>2	0	5 (7.7%)	5 (7.8%)
Patients with previous ectopics			
0	52 (85.2%)	50 (76.9%)	56 (87.5%)
1	6 (9.8%)	6 (9.2%)	4 (6.3%)
2	1 (1.6%)	6 (9.2%)	3 (4.7%)
>2	2 (3.3%)	3 (4.6%)	1 (1.6%)

** SD – Standard Deviation

Appendix 2

Table 3B – Screening serum hormone levels for treated patients in study 2000-02

Serum Hormone	Menopur® IM	Menopur® SC	Repronex® SC
Total patients N	61	64	64
FSH (mIU/mL) Mean (SD**)	6.7 (2.2)	6.9 (2.2)	6.5 (1.8)
Estradiol (pg/mL) Mean (SD**) Range	44.7 (37.2) 10-283	40.8 (20.9) 13-100	42.6 (25.9) 2.5-156

** SD – Standard Deviation

Table 4B – Allocation of patients for Study 2000-02

Number of patients	Menopur® SC	Menopur® IM	Repronex® SC
# Patients randomized and treated with at least one dose of gonadotropin (ITT)	61	65	64
# Patients with Oocyte retrieval (% ITT)	61 (100%)	62 (95%)	62 (97%)
# Patients with Embryos Transfer (% ITT)	57 (93%)	61 (94%)	62 (97%)

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Appendix 2

Table 5B – Key Protocol Violations in study 2000-02

Key Deviations	Menopur® SC (n=61)	Menopur® IM (n=65)	Repronex® SC (n=64)
Patient was found to have uterine fibroids (inclusion deviation)	1	1	2
Receiving a lower dose of leuprolide acetate (GnRHa) than allowed in the protocol	2	1	2
Patient's gonadotropin dose lower than allowed in protocol	0	2	0
Patient was coasted longer than outlined in the protocol (more than 3 days after the last gonadotropin dose)	0	0	1
Patient had "Rescue ICSI" – insemination method performed was not allowed in original protocol	2	1	3
Patient had an hCG dose lower than allowed in the protocol	1	1	2

Appendix 2

Table 6B – Primary efficacy outcome table using the number of total oocytes for the ITT population in study 2000-02

Outcome	Menopur® SC	Menopur® IM	Repronex® SC
Sponsor's Analysis			
n	61	65	64
Mean (SD)*	13.1 (7.2)	13.1 (8.3)	14.4 (7.7)
Median (min, max)	11 (3, 41)	12 (0, 41)	12 (0, 41)
[95% One Sided Confidence Interval around the mean difference from Repronex ®SC]†	**(-4.0, 1.4)**	**(-3.9, 1.4)**	
[95% Two Sided Confidence Interval around the mean difference from Repronex ®SC]**	(-4.4, 1.7)	(-4.3, 1.7)	
Division's Analysis			
n	61	65	64
Mean (SD)*	13.1 (7.2)	13.1 (8.3)	14.4 (7.7)
Median (min, max)	11 (3, 41)	12 (0, 41)	12 (0, 41)
[95% Two Sided Confidence Interval around the mean difference from Repronex® SC]	[-4.5, 1.8]	[-4.3, 1.8]	

† - Sponsor's primary analysis based on Dunnett's procedure for multiple comparisons.

* SD – Standard Deviation

** 95% two-sided confidence interval based on the Dunnett procedure for multiple comparisons.

Appendix 2

Table 7B – Cumulative pregnancy outcomes for study 2000-02 for the treated population

Clinical Outcome	Menopur® SC n(n%)	Menopur® IM n(n%)	Repronex® SC n(n%)
	(n=61)	(n=65)	(n=64)
Total Clinical Pregnancies† n (%)	18 (29.5)	25 (38.5)	24 (37.5%)
Miscarriage	1(1.6)	1(1.5)	0
Ectopic	0	0	1(1.6%)
Livebirth	22	42	36
Singleton births*	8	14	13
Twin births	7	8	7
Triplets births	0	2	1

† Clinical pregnancy defined as a fetal sac with a positive heartbeat
*Includes both full and preterm births

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✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Appendix 3

Table 1A: Incidence of the most common adverse clinical events for study MFK/IVF/0399E in the all-subjects-treated group reported as a percentage of the total population

WHO dictionary included term	Menopur® SC n(n%)*	r-hFSH n(n%)*	r-hFSH† n(n%)*
Total patients	n=373	n=354	n=237
Headache	98 (26.3)	82 (23.2)	44(18.6)
Abdominal Pain	59 (15.8)	59 (16.7)	55(23.2)
Ovarian Hyperstimulation Syndrome	27 (7.2)	20 (5.6)	11 (4.6)
Nausea	38 (10.2)	20 (5.6)	33 (13.9)
Enlarged Abdomen	11 (2.9)	2 (0.6)	3(1.3)
Vomiting	10 (2.7)	8 (2.3)	5(2.1)
Dizziness	10 (2.7)	6 (1.7)	3(1.3)
Back Pain	9 (2.4)	6 (1.7)	4(1.7)
Diarrhea	9 (2.4)	9 (2.5)	1 (0.4)
Pharyngitis	7 (1.9)	8 (2.3)	1 (0.4)
Flatulence	6 (1.6)	8 (2.3)	2 (0.8)
Vaginal Hemorrhage	6 (1.6)	12 (3.4)	0

** n% - patients (%) experiencing adverse events

† Data derived from NDA 21-765/No. 000 – Study 21884

Appendix 3

Table 1B: Incidence of the most common adverse clinical events for study 2000-02 in the all-subjects-treated group reported as a percentage of the total population

WHO dictionary included term	Menopur® SC n(n%)	Menopur® IM n(n%)	Repronex® SC n(n%)
Total patients	n=61	n=65	n=64
Headache	13 (21.3)	12 (18.5)	13 (20.3)
Abdominal Cramps	13 (21.6)	13 (20)	14 (21.9)
Injection Site Reactions	5 (13.5)	4 (10.3)	11 (25)
Abdominal Pain	5 (8.2)	5 (7.7)	4 (6.3)
Ovarian Hyperstimulation Syndrome	1 (1.6)	4 (6.2)	2 (3.1)
Vaginal Spotting	6 (9.8)	8 (12.3)	5 (7.8)
Nausea	6 (9.8)	8 (12.3)	10 (15.6)
Abdominal Fullness	5 (8.2)	6 (9.2)	7 (10.9)
Constipation	5 (8.2)	2 (3.1)	1 (1.6)
Respiratory Disorder	4 (6.6)	5 (7.7)	4 (6.3)
Vomiting	3 (4.9)	3 (4.6)	1 (1.6)
Back Pain	2 (3.3)	1 (1.5)	3 (4.7)
Breast Pain/Tenderness	2 (3.3)	3 (4.6)	5 (7.8)
Dizziness	1 (1.6)	2 (3.1)	3 (4.7)
Diarrhea	1 (1.6)	1 (1.5)	2 (3.1)

** n% - patients (%) experiencing adverse events

Appendix 3

Table 1C: A comparison of incidence of selected adverse clinical events for study 2000-01 in all cycles (all-subjects-treated group) reported as a percentage of the total patient population

WHO dictionary included term	Menopur® SC n(n%)*	Menopur® IM n(n%)*	Repronex® SC n(n%)*
Total patients	n=37	n=39	n=44
Headache	5 (13.5)	7 (17.9)	7 (15.9)
Injection Site Reactions	5 (13.5)	4(10.3)	11(25)
Abdominal Pain	3 (8.1)	7 (15.9)	9 (20.5)
Ovarian Hyperstimulation Syndrome	8 (21.6)	2 (5.1)	4 (9.1)
Nausea	5 (13.5)	1 (2.6)	2 (4.5)
Pelvic Cramps/Discomfort	4 (10.8)	1 (2.6)	1 (2.3)
Vaginal Spotting	3 (8.1)	0	6 (13.6)
Breast Pain/Tenderness	3 (8.1)	0	0
Abdominal Cramps	2 (5.4)	3 (7.7)	9 (20.5)
Abdominal Fullness	2 (5.4)	3 (7.7)	7 (15.9)
Respiratory Disorder	2 (5.4)	1 (2.6)	1 (2.3)
Vomiting	2 (5.4)	0	0

* n% - patients (%) experiencing adverse events

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/s/

Audrey Gassman
10/29/04 05:53:12 PM
MEDICAL OFFICER

Shelley Slaughter
10/29/04 05:57:00 PM
MEDICAL OFFICER
I concur.

Medical Officer's NDA Filing Review

NDA: 21-663 **Serial:**	N-000
Sponsor:	Ferring Pharmaceuticals.
Type of Submission:	Commercial NDA
Trade/Established Names:	Menopur® (Menotropins for injection, USP)
Drug Dosage:	Assisted Reproductive Technology: The recommended initial dose for patients who have received a gonadotropin-releasing hormone (GnRH) antagonist or GnRH agonist is 225 IU. 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 two days and should not exceed 150 IU per adjustment. The maximum daily dose of Menopur® should not exceed 450 IU and dosing beyond 20 days is not recommended.
Strength:	Each vial contains 75 IU of FSH and 75 IU of LH activity.
Routes of Administration:	Delivered by intramuscular (IM) or subcutaneous (SC) injection
Proposed Indications:	Multifollicular development and pregnancy in ART: Menopur® administered subcutaneously or intramuscularly is indicated for the development of multiple follicles and pregnancy in the ovulatory patient participating in an ART program.

Date Submission Received:	December 29, 2003
45 day Filing Meeting held on:	February 5, 2004
Completed:	February 19, 2004
Reviewer:	Audrey Gassman, MD
Related NDA:	21-047 Repronex® (Menotropins for injection, USP)
Related IND:	53,954

Objective: This review is conducted to fulfil a regulatory requirement to review a new drug application for **NDA 21-663** and determine its suitability for filing under 21 CFR 314.101. This document will also serve as the basis for communicating to the sponsor the potential review issues identified during this filing review period.

Conclusion: After preliminary review of the clinical section of this NDA (**21-663**), this reviewer (in conjunction with the statistical reviewer) has noted deficiencies in the statistical section of the submission (See Reviewer's recommendations). If these statistical deficiencies are addressed by the sponsor before filing, there are no significant clinical issues identified that would constitute as the basis for a Refuse-to File action described under 21 CFR 314.101. This reviewer concluded that the application with the deficiencies, at this time, does not permit a substantive clinical review.

Brief Regulatory History:

The sponsor has proposed a new formulation of Repronex® (menotropins for injection, USP) for use in conjunction with human chorionic gonadotropin for multiple follicular development in patients undergoing ART therapy [redacted] Repronex® is a currently approved partially purified preparation of gonadotropin that is extracted from the urine of postmenopausal women. Repronex® contains equal amounts of follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Repronex® was originally approved by the FDA under ANDA 73-598/599 for intramuscular administration as an equivalent of Pergonal® (NDA 17-646). On July 3, 1996 Lederle Laboratories transferred ownership of ANDA 73-598 to Ferring Pharmaceuticals, Inc. IND 53,954 was submitted on August 14, 1997 to study Repronex® for the clinical indications already approved, but administered by the subcutaneous route.

Two phase III clinical studies (97-01 for the indication of ovulation induction in anovulatory women and 97-02 for the indication of multiple follicular development and pregnancy in normally cycling women) were submitted on 28-Oct-03 to NDA 21-047. NDA 21-047 for Repronex® administered by the subcutaneous route was approved on August 27, 1999.

A pre-NDA meeting was held on March 10, 1998 to discuss a planned NDA submission for use of Repronex® administered subcutaneous. At that meeting, the sponsor presented an initial proposal for a "new highly purified" form of Repronex. The Division stated that "an NDA should be submitted for this new purified FSH since this does not appear to be a simple CMC change and clinical studies will be required".

The first protocol submitted for the new purified Repronex® formulation was submitted to IND 53,954 on October 2, 2000 as Study 2000-02 for in vitro fertilization patients (Serial No. 007). The protocol for Study 2000-02 was submitted to IND 53, 954 and reviewed by the Medical Officer on October 5, 2000 (no clinical comments were noted).

The sponsor subsequently submitted a planned pK study protocol (2000-03) for the new purified Repronex in Amendment 008 dated October 20, 2000 to **IND 53,943** (Serial No. 008). A teleconference was held on January 25, 2001 with the sponsor to clarify clinical and chemistry issues for the new purified Repronex® — formulation. The sponsor was informed at the January 2001 teleconference that if the approved Repronex® and the new purified Repronex® — were not bioequivalent as determined by the results of the proposed pK study (2000-03), then safety and efficacy studies would be required for [redacted] ART [redacted] indications. A second protocol [redacted] [as discussed in the teleconference on January 25, 2001] for Repronex® — was submitted to **IND 53,943** on April 6, 2001 and was reviewed by the Medical Officer on April 10, 2001 without comment (Serial No. 15).

A second guidance meeting was held on March 3, 2003 to discuss clinical, biopharmacologic and chemistry issues for the new purified Repronex® submission. At the pre-NDA meeting on March 3, 2003, the sponsor presented their proposed submission for a new formulation of Repronex® with the initial proposed tradename of "Repronex®-— ". The Chemistry Review Team commented that the tradename "Repronex® —— would not be acceptable, and the sponsor should clearly distinguish between the two formulations.

A second bioequivalence study protocol (2003-02) was submitted to IND 53,954 (Serial No. 20) to bridge the formulation of Repronex —® (now referred to as Menopur®) used in study MFK/IVF/0399E with the formulation used in the two studies (2000-01 and 2000-02) performed in the United States. The sponsor stated that the Menopur® formulation used in the two studies performed in the United States would be the formulation for the NDA submission.

The sponsor submitted the complete NDA package on December 29, 2003 for the new formulation of Repronex® with the proposed tradename "Menopur®". Menopur® will have the same indications as Repronex®, (multiple follicular development in patients undergoing ART therapy [ ] and will be administered subcutaneous or intramuscularly.

Reviewer's comments:

1. **A modification to the protocol of Study 2000-02 (labeled Modification #1) was made to the statistical analysis plan on December 1, 2000. This amendment was a) dated after the initiation of the study on September 27, 2000 [although before the study completion date of April 10, 2001] and b) not submitted by the sponsor. Therefore, this protocol modification may be a review issue.**
2. **No protocol or protocol amendments for Study MFK/IVF/0399E were submitted to the IND for review by the Division.**
3. **Study MFK/IVF/0399E had three protocol amendments: Protocol Amendments #1 (dated August 2, 1999), #2 (dated June 14, 1999) and #3 (dated January 1, 2000). These amendments were all dated after the initiation of the study on May 21, 1999. Study MFK/IVF/0399E was completed on November 6, 2000. These protocol amendments may contain review issues.**

Summary of Clinical Data in the NDA Submission:

Efficacy Database: The primary clinical efficacy data consists of two Assisted Reproductive Technology studies (2000-02 [US] and MFK/IVF/0399E [European]) and one [ ] (2000-01 [US]).

- Study 2000-02 was a randomized, active-controlled, parallel-group, open-label study for patients undergoing assisted reproductive technology (ART) treatment. Patients in 2000-02 could have a maximum of one treatment cycle with in vitro fertilization only. A total of 190 patients in study 2000-02 were treated with at least one dose of gonadotropin therapy. Patients were treated with either Menopur® (intramuscularly) or Menopur® (subcutaneously) or the approved Repronex® (subcutaneously). The primary efficacy parameter was number of oocytes retrieved per cycle.
- Study MFK/IVF/0399E was a multi-center, multinational, randomized, open-label study for patients undergoing assisted reproductive technology (ART) treatment. Patients in study MFK/IVF/0399E could have a maximum of one treatment cycle with in vitro fertilization or in vitro fertilization with intracytoplasmic injection (ICSI). A total of 727 patients in study MFK/IVF/0399E were treated with at least one dose of gonadotropin therapy. Patients received down-regulation with a gonadotropin-releasing hormone agonist and were treated with either Menopur® or recombinant follicle stimulating hormone (follitropin alfa). The primary efficacy parameter was ongoing pregnancy after one treatment cycle.

Efficacy Database (continued):

•

Studies 2000-02 and 2000-01 were both conducted in sites in the United States. Study MFK/IVF/0399E was conducted in sites in Europe and Israel. Study MFK/IVF/0399E used a slightly different formulation of Menopur®, and a bioequivalence study was submitted to bridge the U.S. and European formulations (Study 2003-02). Clinical efficacy data derived from the three clinical studies (2000-02, 2000-01 and MFK/IVF/0399E) was included in the labeling information.

Primary Safety Database: The primary safety database includes all subjects in the three clinical trials mentioned above. In this database, the total number of subjects that were treated with Menopur® was:

- 120 patients treated in study 2000-01
-
- 727 patients treated in study MFK/IVF/0399E.

Detailed study reports are provided for all three clinical studies (2000-01, 2000-02 and MFK/IVF/0399E). The adverse event reports for the Menopur® are summarized in the draft label.

Other Databases

PK/PD studies: The Sponsor submitted:

- One pK study (Study 2000-03) for the Menopur® formulation. This bioequivalence study compared the new Menopur® formulation via intramuscular and subcutaneous routes to the currently approved Repronex® formulation. This study was conducted as a multi-center, open-label, randomized, single-dose, two-period cross-over study. The Office of Clinical Pharmacology and Biopharmaceutics is currently reviewing this study
- One bioequivalence study (Study 2003-02) for the Menopur® formulation. This bioequivalence study compared the new Menopur® formulation used in the two United States studies with the Menopur® formulation used in Study MFK/IVF/0399E (the European and Israeli study).

Clinical Review Issues:

a. **Study 2003-02**

- The Biopharmaceutics Division has to determine if the Menopur® formulation used in the United States studies (2000-01 and 2000-02) is equivalent to the Menopur® formulation used in Study MFK/IVF/0399E.

  Reviewer's comment: If the United States formulation (as used in studies 2000-01 and 2000-02) is not bioequivalent to the European formulation, then Study MFK/IVF/0399E will not be an acceptable study for this submission. This is a major review issue.

b. [redacted]

- [redacted]

- [redacted]

Reviewer's comments:

1. [redacted]

2. [redacted]

3. [redacted]

4. [redacted]

5. [redacted]

c. **Study 2002-02**

- The sponsor has defined the primary efficacy endpoint as total oocytes retrieved per cycle. This endpoint was previously agreed to by the Division
- The number of patients (8) with ovarian hyperstimulation in the Menopur® group (administered intramuscularly) appeared to be higher than the other Menopur® group [2 patients] (subcutaneously administered) or the Repronex® group (administered subcutaneously) [2 patients].

Reviewer's comments:

1. **The sponsor did not provide adequate information on the randomization procedure and allocation to allow appropriate analyses by the statistical and medical reviewer in both the paper submission and the electronic SAS transport files**
2. **The current recommendation of the Division is that clinical studies for gonadotropins should be powered for clinical pregnancy, not ovulation rate. Clinical pregnancy rate will be a review issue.**
3. **The sponsor should provide a rationale for the choice of "30% of the expected mean number of oocytes" as the non-inferiority margin for study 2000-02 (US IVF Study).**
4. **This study did not demonstrate non-inferiority in the ITT population as the lower limit of the one-sided 95% confidence interval for Menopur® was not within the stated delta for Repronex®. The sponsor has submitted study MFK/IVF/0399E to further support the non-inferiority of Menopur® to an approved comparator (r-hFSH). Study MFK/IVF/0399E was not reviewed by the Division. The lack of achieving non-inferiority in study 2000-02 will be a major review issue.**
5. **In addition, any significant differences in the treatment groups in terms of ovarian hyperstimulation syndrome or serious adverse events may be review issues.**

a. **Study MFK/IVF/0399E**

- The treatment groups demonstrated some differences in the demographics of the patient populations in terms of duration of infertility and prior unsuccessful treatment cycles. These baseline characteristics will be evaluated with respect to their treatment groups and may be review issues.
- The percentage of patients that were randomized, but prematurely discontinued of 10% was noted on initial review.
- The sponsor's analysis of the primary efficacy endpoint of clinical pregnancy used a one-sided 95% confidence interval that included the lower bound of the confidence interval (-10%).
- A small difference in the percentage of patients with ovarian hyperstimulation was noted between the Menopur® group (7.2%) and the r-FSH group (5.6%).

Reviewer's comments:

1. **The sponsor did not provide adequate information on the randomization procedure and allocation to allow appropriate analyses by the statistical and medical reviewer in both the paper submission and the electronic SAS transport files.**

Reviewer's comments (continued):

2. **The sponsor did not define a rationale for the null hypothesis for this study stating why a 10% difference between the two groups (Menopur® subcutaneously and an approved recombinant follitropin product) would be significant.**
3. **The study included patients with IVF and ICSI. It is unknown what impact this will have on ongoing pregnancy rates.**
4. **This protocol was not reviewed by the Division. The Division will need to further examine the protocol and protocol amendments to see if there are significant review issues.**
5. **Non-inferiority between Menopur® and r-hFSH will be decided on a two-sided 95% confidence interval. This is a review issue.**
6. **In addition, any significant differences in the treatment groups in terms of ovarian hyperstimulation syndrome or serious adverse events may be review issues.**

Reviewer Recommendations:

1. **The deficiencies found in the submitted application make it not acceptable for filing purposes at this time. The sponsor may submit the following items to correct the deficiencies to allow filing:**
    - **Randomization allocation descriptions for each of the three clinical studies (2000-01, 2000-02 and MFK/IVF/0399E)**
    - **Randomization list of all patients randomized for all three clinical studies (2000-01, 2000-02 and MFK/IVF/0399E)**
    - **SAS transport file (RAND.XPT) needs to be re-checked to make sure that all patients that were randomized are linked to a randomization code. This file should be resubmitted if incorrect for all three studies (2000-01, 2000-02 and MFK/IVF/0399E)**
    - **Data listings should be provided for all three studies (2000-01, 2000-02 and MFK/IVF/0399E)**

    These four items will need to be submitted in a timely fashion (one week prior to the filing deadline) to allow review. If the submitted items are adequate, the application will be fileable.
2. **Additional Medical reviewer's comments (#1 through #15) should be sent to the Sponsor, although these do not constitute a filing issue.**

ADDITIONAL COMMENTS TO BE SENT TO THE SPONSOR:

1) **All three clinical studies will be assessed using the ITT population.**
2) **Clinical pregnancy rates will be closely looked at in the review**
3) **A preliminary review of study 2000-02 shows that purified Menopur®, when administered subcutaneously, does not appear to meet the primary efficacy endpoint for mean oocytes retrieved.**
4) **The protocol for MFK/IVF/0399E was not reviewed by the Division. Additional review issues may be noted pending detailed review of protocol, the three protocol amendments and the study data.**
5) **The Medical Reviewer concurs with the Statistician that:**
   - **The sponsor should provide a rationale for the choice of "-10%" as the non-inferiority threshold for Study MFK/IVF/0399E (EU non-inferiority study).**
   - **The sponsor should provide a rationale for the choice of "30% of the expected mean number of oocytes" as the non-inferiority margin for study 2000-02 (US IVF Study).**
   - [ ]
6) **If the United States formulation (as used in studies 2000-01 and 2000-02) is not bioequivalent to the European formulation, then Study MFK/IVF/0399E will not be an acceptable study for this submission. This is a major review issue.**
7) **The Division's position is that non-inferiority will be decided based on a two-sided 95% confidence interval.**
8) **Patient cancellation rates in the three clinical studies may be a review issue.**
9) **The use of ICSI in study MFK/IVF/0399E protocol may be a review issue.**
10) [ ]
11) **Any significant differences in the treatment groups in the three studies, in terms of ovarian hyperstimulation syndrome or serious adverse events, may be review issues.**
12) **The protocol for study MFK/IVF/0399E was not submitted to the Division. It is possible that additional review issues may arise during the review.**

Reviewer's comments (continued):

13) The reviewer asks that the sponsor submit an additional electronic dataset entitled ovarian hyperstimulation syndrome (OHSS) for each study (2000-01, 2000-02 and MFK/IVF/0399E. This dataset should include all patients who had the diagnosis of ovarian hyperstimulation in the study.

The dataset should have the following variables: the patient identifier, treatment group, date of hCG administration (or if none given), serum estradiol at time of hCG (in pg/mL), date of ovarian hyperstimulation first noted, severity of ovarian hyperstimulation, [for IVF studies, include column with the number of oocytes retrieved], whether the patient became pregnant. The sponsor should submit one dataset for each study.

14) The sponsor should resubmit all tables with hormonal values from study MFK/IVF/0399E with estradiol levels in pg/mL and progesterone in ng/mL.

15) For studies 2000-02 and MFK/IVF/0399E provide a dataset with patient identifier, type of gonadotropin agonist used (and dose) and the down-regulated estradiol level (in pg/mL).

16) Please confirm whether Protocol Amendment #1 dated December 1, 2000 for Study 2000-02 was previously submitted to the Division for review.

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

/s/

Audrey Gassman
2/19/04 09:31:47 AM
MEDICAL OFFICER

Shelley Slaughter
2/19/04 10:35:46 AM
MEDICAL OFFICER
I concur.

NDA 21-663

Menopur (menotropins for injection, USP)

Ferring Pharmaceuticals

Safety Update

See MO review Page

10/29/04