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Gonal-F®

(follitropin alfa for injection)

NDA 20-378/S-006

Serono Laboratories

PM: DeGuia

UF Goal Date:
May 27, 2000

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-378/S-006

Serono Laboratories, Inc.
Attention: Thomas A. Lang
Senior Vice President, Regulatory Affairs
100 Longwater Circle
Norwell, MA 02061

MAY 2 4 2000

Dear Mr. Lang:

Please refer to your supplemental new drug application dated July 26, 1999, received July 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Gonal-F® (follitropin alfa for injection).

We acknowledge receipt of your submissions dated August 30, September 1 and November 19, 1999, April 20, May 11 (facsimile), 15, 16 (2) (facsimile) 17, 18 and 23, 2000.

This supplemental new drug application provides for the use of Gonal-F® (follitropin alfa for injection) for induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon draft labeling text (package insert dated May 23, 2000). Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling (package insert dated May 23, 2000).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-378/S-006." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

/S/

Susan Alter, M.D., M.P.H.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Gonal-F®

(follitropin alfa for injection)

For subcutaneous injection

DESCRIPTION

Gonal-F® (follitropin alfa for injection) is a human follicle stimulating hormone (FSH) preparation of recombinant DNA origin, which consists of two non-covalently linked, non-identical glycoproteins designated as the α- and β-subunits. The α- and β-subunits have 92 and 111 amino acids, respectively, and their primary and tertiary structure are indistinguishable from those of human follicle stimulating hormone. Recombinant FSH production occurs in genetically modified Chinese Hamster Ovary (CHO) cells cultured in bioreactors. Purification by immunochromatography using an antibody specifically binding FSH results in a highly purified preparation with a consistent FSH isoform profile, and a high specific activity. The biological activity of follitropin alfa is determined by measuring the increase in ovary weight in female rats. The *in vivo* biological activity of follitropin alfa has been calibrated against the second International Reference Preparation for Human Menopausal Gonadotrophins established in September 1964 by the Expert Committee on Biological Standards of the World Health Organization. Gonal-F® contains no luteinizing hormone (LH) activity. Based on available data derived from physico-chemical tests and bioassays, follitropin alfa and follitropin beta, another recombinant follicle stimulating hormone product, are indistinguishable.

Gonal-F® is a sterile, lyophilized powder intended for subcutaneous injection after reconstitution with Sterile Water for Injection, USP. Each ampule of Gonal-F® contains either 75 IU or 150 IU recombinant FSH, 30 mg sucrose, 1.11 mg dibasic sodium phosphate and 0.45 mg monobasic sodium phosphate monohydrate. O-phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment. Under current storage conditions, Gonal-F® may contain up to 15% of oxidized follitropin alfa.

Therapeutic Class: Infertility

CLINICAL PHARMACOLOGY

Gonal-F® (follitropin alfa for injection) stimulates ovarian follicular growth in women who do not have primary ovarian failure. FSH, the active component of Gonal-F® is the primary hormone responsible for follicular recruitment and development. In order to effect final maturation of the follicle and ovulation in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) must be given following the administration of Gonal-F® when monitoring of the patient indicates that sufficient follicular development has occurred. There is interpatient variability in response to FSH administration. The physicochemical, immunological, and biological activities of recombinant FSH are comparable to those of pituitary and human menopausal urine-derived FSH. Gonal-F® (follitropin alfa for injection), when administered with hCG, stimulates spermatogenesis in men with hypogonadotropic hypogonadism. FSH, the active component of Gonal-F®, is the primary hormone responsible for spermatogenesis.

Pharmacokinetics

Single dose pharmacokinetics of r-hFSH were determined following intravenous, subcutaneous and intramuscular administration of 150 IU Gonal-F® to 12 healthy, down-regulated female volunteers. Steady-state pharmacokinetics were also determined in 12 healthy down-regulated female volunteers who were administered a single daily dose of 150 IU for seven days. These pharmacokinetics were confirmed in pituitary down-regulated women undergoing *in vitro* fertilization and embryo transfer (IVF/ET), treated with FSH doses of up to 450 IU per day. Additionally, single dose pharmacokinetics of r-hFSH were determined following subcutaneous administration of 225 IU Gonal-F® to 12 healthy adult male volunteers in a cross-over design. Steady state pharmacokinetics were also determined in 6 healthy adult male volunteers who were administered a single daily dose of 225 IU Gonal-F® for 7 days. No significant difference in pharmacokinetics is expected in males versus females when administered Gonal-F® subcutaneously. The pharmacokinetic parameters from these studies are included in Table 1.

Table 1: Pharmacokinetic parameters (mean ± SD) of FSH following administration of Gonal-F®

Population	Female				Male	
	Healthy Female Volunteers			IVF/ET Patients	Healthy Male Volunteers	
Dose (IU)	Single Dose IM (150)	Single Dose SC (150)	Multiple Dose SC (7 x 150)	Multiple Dose SC (5 x 225)*	Single Dose SC (225 IU)	Multiple Dose SC (7 x 225 IU)
AUC (IU-hr/L)	206 ± 66	176 ± 87	187 ± 61#	---	220 ± 109	186 ± 23#
C_{max} (IU/L)	3 ± 1	3 ± 1	9 ± 3	---	2.5 ± 0.8	8.3 ± 0.9
t_{max} (hr)	25 ± 10	16 ± 10	8 ± 6	---	20 ± 14	10.7 ± 6.7
$t_{½}$ terminal (hr)	50 ± 27	24 ± 11	24 ± 8	32**	41 ± 14	32 ± 4
CL/F (L/hr)	---	---	---	0.7 ± 0.2	0.86 ± 0.48	0.90 ± 0.12
V/F (L)	---	---	---	10 ± 3	---	---
F (%)	76 ± 30	66 ± 39	---	---	---	---

Abbreviations are: IVF/ET: *in vitro* fertilization/embryo transfer;
C_{max}: peak concentration (above baseline);
t_{max} : time of C_{max};
CL/F: apparent clearance;
V/F: apparent volume of distribution; calculated using a one-compartment model.
$t_{½}$: absorption half-life;
F: bioavailability compared to IV

\# Steady-state $AUC_{144-168}$ (After the 7th daily SC dose)
* First five days of fixed regimen followed by adjustment of the dose depending on response
** increases with body mass index

Absorption

The absorption rate of Gonal-® following subcutaneous or intramuscular administration was found to be slower than the elimination rate. Hence the pharmacokinetics of Gonal-F® are absorption rate-limited.

Distribution

Human tissue or organ distribution of FSH has not been determined for Gonal-F®.
After intravenous administration to pituitary down-regulated, healthy female volunteers, the serum profile of FSH appears to be described by a two compartment open model with a distribution half-life of about 2-2.5 hours. Steady-state serum levels were reached after 4 to 5 days of daily administration.

Metabolism/Excretion

FSH metabolism following administration of Gonal-F® has not been studied in humans. Total clearance after IV administration in healthy females was 0.6 L/hr; mean residence time was 17-20 hours. FSH renal clearance was 0.07 L/hr after intravenous administration representing approximately 1/8 of total clearance.

Pharmacodynamics

Following daily subcutaneous administration of 150 IU of Gonal-F® for 7 days in healthy female volunteers, serum inhibin and estradiol, and total follicular volume responded as a function of time, with pronounced inter-individual variability. Pharmacodynamic effect lagged behind FSH serum concentration. Of the three pharmacodynamic parameters, serum

inhibin levels responded with the least delay and declined rapidly after discontinuation of Gonal-F®. Follicular growth was most delayed and continued even after discontinuation of Gonal-F® administration, and after serum FSH levels had declined. Maximum follicular volume was better correlated with either inhibin or estradiol peak levels than with FSH concentration. Inhibin rise was an early index of follicular development. In healthy male volunteers, despite high interindividual variation and the absence of down-regulation, daily administration of 225 IU Gonal-F® was shown to increase the levels of inhibin to reach a plateau during the whole administration period and then return to baseline.

Population pharmacokinetics and pharmacodynamics

To establish the pharmacokinetics and pharmacodynamics of FSH in a target population, measurements performed during a clinical study of *in vitro* fertilization/embryo transfer were used in conjunction with pharmacokinetic data from studies in healthy female volunteers. The apparent clearance was comparable to that in healthy volunteers. The absorption rate was found to be influenced by the body mass index (BMI), suggesting that the higher the BMI, the lower the rate of absorption. However, FSH serum levels following fixed (during the first five days) and then adjusted doses of Gonal-F® were found to be poor predictors of follicular growth rate. High pre-treatment serum FSH levels may predict lower follicular growth rates.

Special populations: Safety, efficacy, and pharmacokinetics of Gonal-F® in patients with renal or hepatic insufficiency have not been established.

Drug-Drug Interactions: No drug-drug interaction studies have been conducted (see PRECAUTIONS).

Clinical Studies:

Women:

The safety and efficacy of Gonal-F® have been examined in four clinical studies, two studies for ovulation induction and two studies for assisted reproductive technologies (ART). In these comparative studies, there were no clinically significant differences between treatment groups in study outcomes.

1. Ovulation Induction:

The safety and efficacy of Gonal-F® administered subcutaneously vs. urofollitropin administered intramuscularly were assessed in a phase III, open-label, randomized, comparative, multinational, multicenter study in oligo-anovulatory infertile women who failed to ovulate or conceive following adequate clomiphene citrate therapy (Study 5642).

The primary efficacy parameter was the ovulation rate. Two hundred and twenty-two patients entered into the first cycle of treatment, of whom 110 received Gonal-F® and 112 received urofollitropin. Ovulation rates were similar between Gonal-F® and urofollitropin treatment groups. The study results for the 222 patients who received treatment in at least one cycle are summarized in Table 2.

Table 2: Cumulative Patient Ovulation and Clinical Pregnancy Rates by Treatment Group in Ovulation Induction

Study 5642	Gonal-F® (n=110)	urofollitropin (n=112)
Cumulative Ovulation Rate		
cycle 1	64%	59%
cycle 2	78%	82%
cycle 3	84%	91%
Cumulative Clinical Pregnancy* Rate		
cycle 1	21%	21%
cycle 2	28%	38%
cycle 3	35%	46%

* A clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heart activity) was visualized by ultrasound on day 34-36 after hCG administration.

For the 90 patients who had a clinical pregnancy (39 in Gonal-F® group; 51 in urofollitropin group), the outcome of the pregnancy was:

Table 3: Pregnancy Outcome by Treatment Group in Ovulation Induction

Study 5642	Gonal-F® (n=39)	urofollitropin (n=51)
Pregnancies not reaching term	20.5%	13.7%
Single births	74.4%	74.5%
Multiple births	5.1%	11.8%

A second randomized, comparative, open-label, multicenter study was conducted in 23 U.S. centers (Study 5727). The primary efficacy parameter was ovulation rate. Ovulation rates were similar between Gonal-F® and urofollitropin treatment groups. Two hundred and thirty-two patients with oligo-anovulatory infertility received treatment with up to three cycles of Gonal-F® administered subcutaneously (118 patients) or urofollitropin administered intramuscularly (114 patients).

The cumulative patient ovulation rate and clinical pregnancy rates by cycle for the 232 patients who received treatment in at least one cycle.

Table 4: Cumulative Patient Ovulation and Clinical Pregnancy Rates by Treatment Group in Ovulation Induction

Study 5727	Gonal-F® (n=118)	Urofollitropin (n=114)
Cumulative Ovulation Rate		
cycle 1	58%	68%
cycle 2	72%	86%
cycle 3	81%	93%
Cumulative Clinical Pregnancy Rate *		
cycle 1	13%	14%
cycle 2	25%	25%
cycle 3	37%	36%

* A clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heart activity) was visualized by ultrasound on day 34-36 after hCG administration.

For the 85 patients who had a clinical pregnancy (44 in Gonal-F® group; 41 in urofollitropin group), the outcome of the pregnancy is shown in Table 5.

Table 5: Pregnancy Outcome by Treatment Group in Ovulation Induction

Study 5727	Gonal-F® (n=44)	urofollitropin (n=41)
Pregnancies not reaching term	22.7%	22.0%
Single births	63.6%	65.9%
Multiple births	13.7%	12.2%

2. Assisted Reproductive Technologies (ART):

The safety and efficacy of Gonal-F® administered subcutaneously vs. urofollitropin administered intramuscularly were assessed in a phase III, open-label, randomized, comparative, multinational, multicenter study in ovulatory, infertile women undergoing stimulation of multiple follicles for In Vitro Fertilization and Embryo Transfer (IVF/ET) after pituitary down-regulation with a GnRH agonist (Study 5503). The purpose of the study was to demonstrate that Gonal-F®, administered subcutaneously, was clinically not different in terms of safety and efficacy from urofollitropin, administered intramuscularly. The initial and maximal doses of Gonal-F® were 225 and 450 IU, respectively. The primary efficacy parameter was the number of mature pre-ovulatory follicles on the day of hCG administration. One hundred and twenty-three patients were randomized and received either Gonal-F® (60 patients) or urofollitropin (63 patients).

The results summarized in Table 6 are mean data with Gonal-F® and urofollitropin administered to ovulatory infertile women undergoing multiple follicular development for IVF/ET.

Table 6: Treatment Outcomes by Treatment Group in ART

Study 5503	Gonal-F® (n=60)	urofollitropin (n=63)
Mean number of follicles ≥ 14mm diameter on day of hCG	7.8	9.2
Mean number of oocytes recovered per patient	9.3	10.7
Mean Serum E2 (pg/mL) on day of hCG	1576	2193
Mean treatment duration in days (range)	9.9 (5-20)	9.4 (5-14)
Clinical pregnancy* rate per attempt	20%	16%
Clinical pregnancy* rate per embryo transfer	24%	19%

* A clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heart activity) was visualized by ultrasound on day 34-36 after hCG administration.

For the 22 patients who had a clinical pregnancy (12 in Gonal-F® group; 10 in urofollitropin group), the outcome of the pregnancy is shown in Table 7.

Table 7: Pregnancy Outcome by Treatment Group in ART

Study 5503	Gonal-F® (n=12)	Urofollitropin (n=10)
Pregnancies not reaching term	25.0%	20.0%
Single births	41.7%	50.0%
Multiple births	33.3%	30.0%

A second randomized, comparative, open-label, multicenter study was conducted in 7 U.S. centers (Study 5533). One hundred and fourteen patients with ovulatory infertility undergoing IVF/ET were randomized and received either Gonal-F® by subcutaneous administration (56 patients) or urofollitropin by intramuscular administration (58 patients) following pituitary down-regulation with a GnRH agonist. The primary efficacy parameter was the number of mature pre-ovulatory follicles on the day of hCG administration. Results are summarized in Table 8.

Table 8: Treatment Outcomes by Treatment Group in ART

Study 5533	Gonal-F® (n=56)	urofollitropin (n=58)
Mean number of follicles ≥ 14mm diameter on day of hCG	7.2	8.3
Mean number of oocytes recovered per patient	9.3	12.3
Mean Serum E2 (pg/mL) on day of hCG	1236	1513
Mean treatment duration in days (range)	10.1(5-15)	9.0 (5-12)
Clinical pregnancy* rate per attempt	21%	22%
Clinical pregnancy* rate per embryo transfer	26%	25%

* A clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heart activity) was visualized by ultrasound on day 34-36 after hCG administration.

For the 25 patients who had a clinical pregnancy (12 in Gonal-F® group; 13 in urofollitropin group), the outcome of the pregnancy is shown in Table 9.

Table 9: Pregnancy Outcome by Treatment Group in ART

Study 5533	Gonal-F® (n=12)	urofollitropin (n=13)
Pregnancies not reaching term	33.3%	30.8%
Single births	41.7%	38.5%
Multiple births	25.0%	30.8%

Men:

The safety and efficacy of Gonal-F® administered concomitantly with hCG have been examined in three open-label clinical studies for induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism.

The three multicenter studies involved three to six months of pretreatment with chorionic gonadotropin for injection (Profasi®) to normalize serum testosterone levels, followed by 18 months of treatment with Gonal-F® and hCG. The objective of each study was induction of spermatogenesis (a sperm density of $\geq 1.5 \times 10^6$/mL).

Study 5844 enrolled 32 patients in six centers in the United Kingdom, France and Germany. The second trial, Study 6410, was conducted in Australia and enrolled 10 patients in two centers. Study 6793, conducted in 7 centers in the United States, was planned to enroll 32 patients. The interim data for the US study includes 30 of the planned 32 patients. For all 3 studies, a total of 72 patients were enrolled and received hCG and 56 of those patients entered the Gonal-F® treatment phase of the trials.

The populations enrolled in the three studies were similar: Study 5844 studied a naïve population who had had no prior treatment with gonadotropins; mean age was 25.9 (range 16 to 48) years, mean (± SD) testis volume was 2.0 ± 1.2 mL, and 12 of the 32 patients (37.5%) were anosmic. Thirty one of the patients were Caucasian and one was Asian. In Study 6410, mean age was 36 (range 26 to 48) years, , 6 and 1 of the 10 patients had previously been treated with gonadotropins and GnRH, respectively; mean testis volume was 4.5 ± 2.9 mL; and 2 of the 10 patients (20%) were anosmic. Seven patients were Caucasian and three were Asian. In the 30 patients reported in the interim analysis of Study 6793, the mean age was 30.1 (range 22 to 44) years; 4 and 3 of the 30 patients had been treated with gonadotropins and GnRH, respectively, in the past; mean testis volume was 4.4 ± 1.3 mL; and 10 of the 30 patients (33.3%) were anosmic. Twenty five of the patients were Caucasian, three were Asian, and one each of Moroccan and Indian ancestry.

The primary efficacy endpoint of all three studies was the achievement of a sperm density $\geq 1.5 \times 10^6$/mL. The study results for the patients treated with Gonal-F® and hCG are summarized in Table 10.

Table 10: Number of Men Receiving Gonal-F® Who Achieved a Sperm Density ≥ 1.5 x 10^6/mL

	Study 5844 (n=26)	Study 6410 (n=8)	Study 6793 (n=22) *
Sperm Concentration ≥ 1.5 x 10^6/mL			
Yes	12 (46.2%)	5 (62.5%)	14 (63.6%)
No	14 (53.8%)	3 (37.5%)	8 (36.4%)
95% Confidence Interval	(26.6% - 66.6%)	(24.5% - 91.5%)	(40.7% - 82.8%)

* Interim data

The time to achievement of the primary efficacy endpoint is summarized in Table 11.

Table 11: Time to Achievement of Sperm Density ≥ 1.5 x 10^6/mL in Men Receiving Gonal-F®

	Study 5844 (n=26)	Study 6410 (n=8)	Study 6793 (n=22) *
Number of Men Achieving Sperm Concentration			
n	12	5	14
Time (Months) to Sperm Concentration ≥ 1.5 x 10^6/mL			
Median	12.4	9.1	6.8
Range	(2.7 – 18.1)	(8.8 – 11.7)	(2.8 – 15.7)

* Interim data

220 **Table 12: Pregnancy Outcome in Partners of Men Desiring Fertility**

	Study 5844 (n=7)	Study 6410 (n=10)	Study 6793 (n=20) *
Pregnancy	6 (86%)	3 (30%)	3 (15%)
Pregnancy not reaching term	1 (14%)	1 (10%)	2 (10%)
Single births	5 (71%)	2 (20%)	1 (5%)

221 * Interim data

222 Of the 56 patients who received Gonal-F® in Studies 5844, 6410, and 6793, 12 pregnancies
223 were achieved in 10 partners of the 37 patients who were seeking pregnancy and who
224 currently had a partner during the studies. Thus, pregnancy (clinical and chemical) was
225 documented to have been achieved by 27% of the patients' partners seeking pregnancy
226 during the exposure period to Gonal-F® in the 3 trials. Eight pregnancies continued to term,
227 and 8 healthy babies were born to 7 couples as a result of those studies.

228 **INDICATIONS AND USAGE**

229 ***Women:*** Gonal-F® (follitropin alfa for injection) is indicated for the induction of
230 ovulation and pregnancy in the anovulatory infertile patient in whom the cause of infertility
231 is functional and not due to primary ovarian failure. Gonal-F® is also indicated for the
232 development of multiple follicles in the ovulatory patient participating in an Assisted
233 Reproductive Technology (ART) program.

Selection of Patients:

1. Before treatment with Gonal-F® is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy. Patients with tubal obstruction should receive Gonal-F® only if enrolled in an *in vitro* fertilization program.

2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.

3. Appropriate evaluation should be performed to exclude pregnancy.

4. Patients in later reproductive life have a greater predisposition to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting Gonal-F® therapy.

5. Evaluation of the partner's fertility potential should be included in the initial evaluation.

Men: Gonal-F® (follitropin alfa for injection) is indicated for the induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in whom the cause of infertility is not due to primary testicular failure.

Selection of Patients:

1. Before treatment with Gonal-F® is instituted for azoospermia, a thorough medical and endocrinologic evaluation must be performed.

2. Hypogonadotropic hypogonadism should be confirmed, and primary testicular failure should be excluded by the determination of gonadotropin levels.

3. Prior to Gonal-F® therapy for azoospermia in patients with hypogonadotropic hypogonadism, serum testosterone levels should be normalized.

CONTRAINDICATIONS

Gonal-F® (follitropin alfa for injection) is contraindicated in women and men who exhibit:

1. Prior hypersensitivity to recombinant FSH preparations or one of their excipients.
2. High levels of FSH indicating primary gonadal failure.
3. Uncontrolled thyroid or adrenal dysfunction.
4. Sex hormone dependent tumors of the reproductive tract and accessory organs.
5. An uncontrolled organic intracranial lesion such as a pituitary tumor.

And in women who exhibit

6. Abnormal uterine bleeding of undetermined origin (see "Selection of Patients").
7. Ovarian cyst or enlargement of undetermined origin (see "Selection of Patients").
8. Pregnancy.

WARNINGS

Gonal-F® (follitropin alfa for injection) should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonal-F® is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and requires the availability of appropriate monitoring facilities (see "Precautions/ Laboratory Tests"). Safe and effective use of Gonal-F® in women requires monitoring of ovarian response with serum estradiol and vaginal ultrasound on a regular basis. The lowest effective dose should be used.

Overstimulation of the Ovary During FSH Therapy:

Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distention and/or abdominal pain occurs in approximately 20% of those treated with urofollitropin and hCG, and generally regresses without treatment within two or three weeks. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Gonal-F® therapy, hCG should not be administered in this course of therapy. This will reduce the chances of development of Ovarian Hyperstimulation Syndrome.

Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical event distinct from uncomplicated ovarian enlargement. Severe OHSS may progress rapidly (within 24 hours to

several days) to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see "Pulmonary and Vascular Complications"). Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with Ovarian Hyperstimulation Syndrome (OHSS).

OHSS occurred in 9 of 228 (3.9%) Gonal-F® treated women during ovulation induction clinical trials and of this number, 1 of 228 (0.4%) was classified as severe. In ART clinical studies, OHSS occurred in 0 of 116 (0.0%) Gonal-F® treated women. OHSS may be more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore, patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration (see "Precautions/Laboratory Tests"), the hCG must be withheld.

If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized.

A physician experienced in the management of this syndrome, or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

Pulmonary and Vascular Complications:
Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome and exacerbation of asthma) have been reported. In addition, thromboembolic events both in association with, and separate from Ovarian Hyperstimulation Syndrome have been reported. Intravascular thrombosis and embolism can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple Births: Reports of multiple births have been associated with Gonal-F® treatment. In ovulation induction clinical trials, 12.3% of live births were multiple births in women receiving Gonal-F® and 14.5% of live births were multiple births in women receiving urofollitropin. In IVF/ET clinical trials, 44.0% of live births were multiple births in women receiving Gonal-F® and 41.0% of live births were multiple births in women receiving urofollitropin and is dependent on the number of embryos transferred. The patient should be advised of the potential risk of multiple births before starting treatment.

PRECAUTIONS

General: Careful attention should be given to the diagnosis of infertility in candidates for Gonal-F® (follitropin alfa for injection) therapy (see "Indications and Usage/ Selection of Patients").

Information for Patients: Prior to therapy with Gonal-F®, patients should be informed of the duration of treatment and monitoring of their condition that will be required. The risks of ovarian hyperstimulation syndrome and multiple births in women (see **WARNINGS**) and other possible adverse reactions (see "**Adverse Reactions**") should also be discussed.

Laboratory Tests: In most instances, treatment of women with Gonal-F® results only in follicular recruitment and development. In the absence of an endogenous LH surge, hCG is given when monitoring of the patient indicates that sufficient follicular development has occurred. This may be estimated by ultrasound alone or in combination with measurement of serum estradiol levels. The combination of both ultrasound and serum estradiol measurement are useful for monitoring the development of follicles, for timing of the ovulatory trigger, as well as for detecting ovarian enlargement and minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation. It is recommended that the number of growing follicles be confirmed using ultrasonography because plasma estrogens do not give an indication of the size or number of follicles.

The clinical confirmation of ovulation, with the exception of pregnancy, is obtained by direct and indirect indices of progesterone production. The indices most generally used are as follows:

1. A rise in basal body temperature;
2. Increase in serum progesterone; and
3. Menstruation following a shift in basal body temperature.

When used in conjunction with the indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:

1. Fluid in the cul-de-sac;
2. Ovarian stigmata;
3. Collapsed follicle; and
4. Secretory endometrium.

Accurate interpretation of the indices of follicle development and maturation require a physician who is experienced in the interpretation of these tests.

Drug Interactions: No drug/drug interaction studies have been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Gonal-F®. However, r-hFSH showed no mutagenic activity in a series of tests performed to evaluate its potential genetic toxicity including, bacterial and mammalian cell mutation tests, a chromosomal aberration test and a micronucleus test.

Impaired fertility has been reported in rats, exposed to pharmacological doses of r-hFSH (≥ 40 IU/kg/day) for extended periods, through reduced fecundity.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse

reactions in the nursing infant from Gonal-F®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Women: The safety of Gonal-F® was examined in four clinical studies that enrolled 691 patients into two studies for ovulation induction (454 patients) and two studies for ART (237 patients).

Adverse events occurring in more than 10% of patients were headache, ovarian cyst, nausea, and upper respiratory tract infection in the US ovulation induction study and headache in the US ART study. Adverse events (without regard to causality assessment) occurring in at least 2% of patients are listed in Table 13 and Table 14.

385
386

Table 13: US Controlled Trial in Ovulation Induction, Study 5727

Body System Preferred Term	Gonal-F® Patients (%) Experiencing Events Treatment cycles = 288* n=118	urofollitropin Patients (%) Experiencing Events Treatment cycles = 277 n= 114
Reproductive, Female		
Intermenstrual Bleeding	9.3%	4.4%
Breast Pain Female	4.2%	6.1%
Ovarian Hyperstimulation**	6.8%	3.5%
Dysmenorrhea	2.5%	6.1%
Ovarian Disorder	1.7%	2.6%
Cervix Lesion	2.5%	0.9%
Menstrual Disorder	2.5%	0.9%
Gastro-intestinal System		
Abdominal Pain	9.3%	12.3%
Nausea	13.6%	3.5%
Flatulence	6.8%	8.8%
Diarrhea	7.6%	3.5%
Vomiting	2.5%	2.6%
Dyspepsia	1.7%	3.5%
Central and Peripheral Nervous System		
Headache	22.0%	20.2%
Dizziness	2.5%	0.0%
Neoplasm		
Ovarian Cyst	15.3%	28.9%
Body as a Whole- General		
Pain	5.9%	6.1%
Back Pain	5.1%	1.8%
Influenza-like Symptoms	4.2%	2.6%
Fever	4.2%	1.8%
Respiratory System		
Upper Respiratory Tract Infection	11.9%	7.9%
Sinusitis	5.1%	5.3%
Pharyngitis	2.5%	3.5%
Coughing	1.7%	2.6%
Rhinitis	0.8%	2.6%
Skin and Appendages		
Acne	4.2%	2.6%

Psychiatric		
Emotional Lability	5.1%	2.6%
Urinary System		
Urinary Tract Infection	1.7%	4.4%
Resistance Mechanism		
Moniliasis Genital	2.5%	0.9%
Application Site		
Injection Site Pain	2.5%	0.9%

* up to 3 cycles of therapy

** Severe = 0.8% of 118 patients in Study 5727

Additional adverse events not listed in Table 13 that occurred in 1 to 2% of Gonal-F® treated patients in the US ovulation induction study included the following: leukorrhea, vaginal hemorrhage, migraine, fatigue, asthma, nervousness, somnolence, and hypotension.

Table 14: US Controlled Trial in ART, Study 5533

Body System Preferred Term	Gonal-F® Patients (%) Experiencing Events n=59	urofollitropin Patients (%) Experiencing Events n= 61
Reproductive, Female		
Intermenstrual Bleeding	3.6%	5.2%
Leukorrhea	1.7%	3.4%
Vaginal Hemorrhage	3.6%	3.4%
Gastro-intestinal System		
Nausea	5.4%	1.7%
Flatulence	3.6%	0.0%
Central and Peripheral Nervous System		
Headache	12.5%	3.4%
Body as a Whole- General		
Abdominal Pain	8.9%	3.4%
Pelvic Pain Female	7.1%	1.7%
Respiratory System		
Upper Respiratory Tract Infection	3.6%	1.7%
Metabolic and Nutritional		
Weight Increase	3.6%	0.0%

Additional adverse events not listed in Table 14 that occurred in 1 to 2% of Gonal-F® treated patients in the US Assisted Reproductive Technology (ART) study included the following: D&C following delivery or abortion, dysmenorrhea, vaginal hemorrhage, diarrhea, tooth disorder, vomiting, dizziness, paraesthesia, abdomen enlarged, chest pain, fatigue, dyspnea, anorexia, anxiety, somnolence, injection site inflammation, injection site reaction, pruritus, pruritus genital, myalgia, thirst, and palpitation.

Two additional clinical studies (for ovulation induction and ART, respectively) were conducted in Europe. The safety profiles from these two studies were comparable to that of the data presented above.

The following medical events have been reported subsequent to pregnancies resulting from Gonal-F® therapy in controlled clinical studies:

1. Spontaneous Abortion
2. Ectopic Pregnancy
3. Premature Labor
4. Postpartum Fever
5. Congenital abnormalities

Two incidents of congenital cardiac malformations have been reported in children born following pregnancies resulting from treatment with Gonal-F® and hCG in Gonal-F® clinical studies 5642 and 5727. In addition, a pregnancy occurring in study 5533 following treatment with Gonal-F® and hCG was complicated by apparent failure of intrauterine growth and terminated for a suspected syndrome of congenital abnormalities. No specific diagnosis was made. The incidence does not exceed that found in the general population.

The following adverse reactions have been previously reported during menotropin therapy:

1. Pulmonary and vascular complications (see "Warnings"),
2. Adnexal torsion (as a complication of ovarian enlargement),
3. Mild to moderate ovarian enlargement,
4. Hemoperitoneum

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

Men:

The safety of Gonal-F® was examined in 3 clinical studies that enrolled 72 patients for induction of spermatogenesis and fertility of whom 56 patients received Gonal-F®. One hundred and twenty-three adverse events, including 7 serious events, were reported in 34 of the 56 patients during Gonal-F® treatment.

In Study 5844, 21 adverse events, including 4 serious adverse events, were reported by 14 of the 26 patients (53.8%) treated with Gonal-F®. Events occurring in more than one patient were varicocele (4) and injection site reactions (4). The 4 serious adverse events were testicular surgery for cryptorchidism, which existed prestudy, hemoptysis, an infected pilonidal cyst, and lymphadenopathy associated with an Epstein-Barr viral infection.

In Study 6410, 3 adverse events were reported in 2 of the 8 patients (24%) treated with Gonal-F®. One serious adverse event was reported, surgery for gynecomastia which existed at baseline.

In the interim analysis of Study 6793, 18 of 22 patients (81.8%) reported a total of 99 adverse events during Gonal-F® treatment. The most common events of possible, probable, or definite relationship to study drug therapy occurring in more than 2 patients were: acne (25 events in 13 patients ; 59% of patients); breast pain (4 events in 3 patients ; 13.6% of patients); and fatigue, gynecomastia, and injection site pain (each of which was reported as 2 events by 2 patients ; 9.1% of patients). Two serious adverse events (hospitalization for drug abuse and depression) were reported by a single patient in the interim analysis.

A total of 12,026 injections of Gonal-F® were administered by the 56 patients who received Gonal-F® in Studies 5844, 6410, and 6793 combined. The injections were well-tolerated, with no or mild reactions (redness, swelling, bruising and itching) reported by patients for 93.3% of injections. Moderate and severe reactions, consisting primarily of pain, were reported for 4.8% of injections, and no self-assessment was available for 1.9% of injections.

OVERDOSAGE

Aside from possible ovarian hyperstimulation and multiple gestations (see "Warnings"), there is no information on the consequences of acute overdosage with Gonal-F® (follitropin alfa for injection).

DOSAGE AND ADMINISTRATION

Dosage:

Infertile Patients with oligo-anovulation: The dose of Gonal-F® (follitropin alfa for injection) to stimulate development of the follicle must be individualized for each patient.

The lowest dose consistent with the expectation of good results should be used. Over the course of treatment, doses of Gonal-F® may range up to 300 IU per day depending on the individual patient response. Gonal-F® should be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. A response is generally evident after 5 to 7 days. Subsequent monitoring intervals should be based on individual patient response.

It is recommended that the initial dose of the first cycle be 75 IU of Gonal-F® per day, ADMINISTERED SUBCUTANEOUSLY. An incremental adjustment in dose of up to 37.5 IU may be considered after 14 days. Further dose increases of the same magnitude could be made, if necessary, every seven days. Treatment duration should not exceed 35 days unless an E2 rise indicates imminent follicular development. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, chorionic gonadotropin, hCG, (5,000 USP Units) should be given 1 day after the last dose of Gonal-F®. Chorionic gonadotropin should be withheld if the serum estradiol is greater than 2,000 pg/mL. If the ovaries are abnormally enlarged or abdominal pain occurs, Gonal-F® treatment should be discontinued, hCG should not be administered, and the patient should be advised not to have intercourse; this may reduce the chance of development of the Ovarian Hyperstimulation Syndrome and, should spontaneous ovulation occur, reduce the chance of multiple gestation. A follow-up visit should be conducted in the luteal phase.

The initial dose administered in the subsequent cycles should be individualized for each patient based on her response in the preceding cycle. Doses larger than 300 IU of FSH per day are not routinely recommended. As in the initial cycle, 5,000 USP Units of hCG must be given 1 day after the last dose of Gonal-F® to complete follicular development and induce ovulation. The precautions described above should be followed to minimize the chance of development of the Ovarian Hyperstimulation Syndrome.

The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational activity. Care should be taken to ensure insemination. In light of the indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Gonal-F®.

Assisted Reproductive Technologies: As in the treatment of patients with oligo-anovulatory infertility, the dose of Gonal-F® to stimulate development of the follicle must be individualized for each patient. For Assisted Reproductive Technologies, therapy with Gonal-F® should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU per day, until sufficient follicular development is attained. In most cases, therapy should not exceed ten days.

In patients undergoing ART, whose endogenous gonadotropin levels are suppressed, Gonal-F® should be initiated at a dose of 225 IU per day. Treatment should be continued until adequate follicular development is indicated as determined by ultrasound in combination with measurement of serum estradiol levels. Adjustments to dose may be considered after five days based on the patient's response; subsequently dosage should be

adjusted no more frequently than every 3-5 days and by no more than 75-150 IU additionally at each adjustment. Doses greater than 450 IU per day are not recommended. Once adequate follicular development is evident, hCG (5,000 to 10,000 USP Units) should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing OHSS.

Male Patients with Hypogonadotropic Hypogonadism

The dose of Gonal-F® (follitropin alfa for injection) to induce spermatogenesis must be individualized for each patient.

Gonal-F® must be given in conjunction with hCG. Prior to concomitant therapy with Gonal-F® and hCG, pretreatment with hCG alone (1,000 to 2,250 USP Units two to three times per week) is required. Treatment should continue for a period sufficient to achieve serum testosterone levels within the normal range. Such pretreatment may require 3 to 6 months and the dose of hCG may need to be increased to achieve normal serum testosterone levels.

After normal serum testosterone levels are reached, the recommended dose of Gonal-F® is 150 IU administered subcutaneously three times a week and the recommended dose of hCG is 1,000 USP Units (or the dose required to maintain serum testosterone levels within the normal range) three times a week. The lowest dose of Gonal-F® which induces spermatogenesis should be utilized. If azoospermia persists, the dose of Gonal-F® may be

519 increased to a maximum dose of 300 IU three times per week. Gonal-F® may need to be
520 administered for up to 18 months to achieve adequate spermatogenesis

521

522 **Administration:**

523 Dissolve the contents of one or more ampules of Gonal-F® in one-half to one mL of Sterile
524 Water for Injection, USP (concentration should not exceed 225 IU/0.5 mL) and
525 ADMINISTER SUBCUTANEOUSLY immediately. Any unused reconstituted material
526 should be discarded.

527 Parenteral drug products should be inspected visually for particulate matter and discoloration
528 prior to administration, whenever solution and container permit.

529 ***HOW SUPPLIED***

530 Gonal-F® (follitropin alfa for injection) is supplied in a sterile, lyophilized form in single
531 dose ampules containing 75 or 150 IU FSH activity. The following package combinations
532 are available:

533 - 1 ampule 75 IU Gonal-F® and 1 ampule 1 mL Sterile Water for Injection, USP, NDC
534 44087-9075-1
535 - 10 ampules 75 IU Gonal-F® and 10 ampules 1 mL Sterile Water for Injection, USP,
536 NDC 44087-9075-3
537 - 100 ampules 75 IU Gonal-F® and 100 ampules 1 mL Sterile Water for Injection, USP,
538 NDC 44087-9075-4

- 1 ampule 150 IU Gonal-F® and 1 ampule 1 mL Sterile Water for Injection, USP, NDC 44087-9150-1

Lyophilized ampules may be stored refrigerated or at room temperature (2°-25°C/36°-77°F). Protect from light. Use immediately after reconstitution. Discard unused material.

Caution: Federal law prohibits dispensing without prescription.

Manufactured for:
SERONO LABORATORIES, INC.
Randolph, MA 02368 USA

by: Laboratoires Serono SA
Aubonne, Switzerland

Revised: *May 2000*

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May 17, 2000

Susan Allen, M.D.
Acting Director
Division of Reproductive and Urologic Drug
Products, HFD-580 (Room 17-B-45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Response to Information Request

Dear Dr. Allen:

Reference is made to NDA 20-378 for Gonal-F® (follitropin alfa for injection) approved on September 29, 1997. Reference is also made to our supplemental New Drug Application (S-006) dated July 26, 1999, which provides for revised labeling to include a new indication; namely, administration of Gonal-F® with concommitant chorionic gonadotropin for the stimulation of spermatogenesis in men who have primary or secondary hypogonadotropic hypogonadism.

Further reference is made to a request from the Division on May 10, 2000 for patent information relevant to this supplemental application. Accordingly, this letter provides confirmation that Serono currently has no patent related to the use of Gonal-F® in males for this indication.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of Code of Federal Regulations.

Should you have any concerns about this submission, please contact me at (781)-681-2298 or Debbie DeMuria, Pharm.D., Sr. Regulatory Affairs Associate at (781) 681-2267.

Sincerely,

Pamela Williamson-Joyce
Vice President, Regulatory Affairs

cc: Eufrecina DeGuia: Desk Copy

Exclusivity Summary Form

EXCLUSIVITY SUMMARY FOR NDA # 20-378 SUPPL # 006

Trade Name: Gonal-F **Generic Name: follitropin alfa for injection**

Applicant Name: Serono Laboratories HFD # 580

Approval Date If Known: May 24, 2000

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. **An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.**

   a) **Is it an original NDA?**

   YES/___/ NO /_X_/

   b) **Is it an effectiveness supplement?**

   YES /_X__/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _SE1_____

   c) **Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")**

   YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 8/27/97
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /__X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO - please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES.
(Answer either #1 or #2 as appropriate)

1. **Single active ingredient product.**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _20-378 _____Gonal –F (follitropin alfa for injection)_____

NDA# _20-582_____Follistim (follitropin beta for injection)_____

NDA# _____ _____

2. **Combination product.**

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS.

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations?
(The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_ __/ NO /_X__/

(1) **If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.**

YES /___/ NO /_X_/

If yes, explain:

(2) **If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?**

YES /___/ NO /_X__/

If yes, explain:

(c) **If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval: Clinical Trials GF 6793, 5844, 6410**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. **In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.**

a) **For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")**

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) **For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?**

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

(c) **If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):**

_GF 6793_____ GF 6410_____

_GF 5844_____ _____

4. **To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.**

a) **For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?**

Investigation #1

IND # 38, 712_____ YES /_X__/ NO /___/ Explain: _____

Investigation #2

IND # _43,865___ YES /_X__/ NO /___/ Explain: _____

b) **For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?**

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) **Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)**

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature /S/ **Date:** May 12, 2000

Title: Regulatory Project Manager

Signature of Office/Division Director

Signature: /S/ **Date:** 5/14/00

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

BLA # 20-378 Supplement # 006 Circle one: (SE1) SE2 SE3 SE4 SE6

HFD 580 Trade and generic names/dosage form: Gonal-F (follitropin alfa for injection) Action: (AP) AE NA

Applicant: Serono Laboratories, Inc. Therapeutic Class: Infertility

Indication(s) previously approved: Assisted Reproductive Technology (ART) and Ovulation Induction
Pediatric information in labeling of approved indication(s) is adequate __ inadequate __ N/A
Proposed indication in this application: Male Hypogonadotropic Hypogonadism

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) _X__ No (Sign and return the form)
WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)
___Neonates (Birth-1 month) __ Infants (1month-2yrs) __Children (2-12yrs) ___ Adolescents (12-16 yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing.
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__X_ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___ No N/A
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer's memo dated May 17, 2000. (e.g., medical review, medical officer, team leader)

/S/
Signature Of Preparer And Title

MAY 19, 2000
Date

CC: ORIG NDA # 20-378/S-006
HF_580/DIV FILE
NDA/ACTION PACKAGE
HFD-006/ KROBERTS

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

MEMORANDUM

To: NDA 20378 – supplement S-006

From: George S. Benson. MD (ISI) 5/17/00
Medical Officer

Date: May 17, 2000

Re: 1) Labelling deficiencies
2) Pediatric use

1) Labelling deficiencies: Three labelling issues were previously unresolved:
   a) The dose of hCG and possible dose escalation to achieve normal testosterone levels were not clearly addressed.
   b) The dose escalation of Gonal-F in patients with persistent azoospermia was not clearly addressed.
   c) It was not clear whether or not IU and U USP are equivalent units for hCG.

All three of these issues have been resolved. The label has been changed to clarify a) and b). The dosage units are equivalent and the label has been clarified using "USP Units".

2) Pediatric studies are not needed. Gonal-F has received orphan drug status and is indicated for the induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism (HH) and in whom the cause of infertility is not due to primary testicular failure. The drug is indicated only for azoospermia and infertility and not for other symptoms of HH. This drug product has little or no potential for use in pediatric patients.

CC: Susan Allen. MD
Marianne Mann. MD
Mark Hirsch. MD
Dan Shames. MD
Freshnie DeGuia

16. DEBARMENT CERTIFICATION

Debarment Certification Statement

In accordance with Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the undersigned hereby certifies that Serono Laboratories, Inc. did not and will not use in any capacity the services of any person debarred under sections (a) or (b) [section 306 (a) or (b)], in connection with this application.

Rosann J. Reinhart
Executive Director, Regulatory Affairs

23 July 99
Date

U.S. GOVERNMENT MEMORANDUM

DATE: May 19, 2000

TO: Eufrecinia DeGuia, CSO, HFD-580, DRUDP

FROM: Roy Blay, Ph.D., GCPB1, DSI RB 5/19/00

THROUGH: David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations

SUBJECT: NDA 20-378/S-006, Gonal-F, Inspection Status

The original inspections were for:

Alvin Matsumoto, M.D.
182b V.A. Medical Center
1660 South Columbian Way
Seattle, WA 98108
PROTOCOL #6793

The letter for Dr. Matsumoto is completed and was signed by Dr. Lepay on May 19, 2000. The inspection was classified VAI as the result of a minor protocol violation. A copy of this letter is being forwarded to you today.

A letter for has not been prepared as the EIR has not been received from the District Office. The inspection was completed and a 483 issued to the ——— on April 25, 2000. I received a facsimile of the 483 on the same day. The 483 cites instances where the clinical investigator failed to keep adequate and accurate records and failed to adhere to the protocol in specific instances. Based *only* on the 483, I believe that the letter to ——— will be classified VAI.

It is my understanding that an Action Package for this application is being prepared for review and signature this coming Wednesday (May 24, 2000). For the reasons outlined above, a thorough evaluation of the inspection report fo ——— has not been completed and cannot be completed until the EIR is received and reviewed in its entirety.

Overall Summary

While preliminary, it is my assessment based on information currently available that data from these two inspections are acceptable for use by HFD-580.

CONCURRENCE:

Concur: ISI Date: 5/23/00

Nonconcur: _____ Date: _____

(See attached supervisory comments regarding non-concurrence)

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations

cc:
HFD-580/NDA 20-378/S-006
HFD-580/DeGuia
HFD-580/
HFD-46/Blay

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: May 23, 2000 LLP 5/23/00

From: Lana L. Pauls, M.P.H.
Associate Director, Division of Reproductive and Urologic Drug Products (HFD-580)

Subject: Review of Financial Disclosure documents

To: The file (NDA 20-378)

I have reviewed the financial disclosure information submitted by Serono Laboratories, Inc. in support of their supplemental NDA, NDA 20-378/S-006.

Three studies were conducted to support the safety and efficacy of Gonal-F (follitropin alfa for injection) for the treatment of male hypogonadotropic hypogonadism. The study numbers and their respective outcomes with regard to financial disclosure obligations are summarized below:

Study No.	Study Status	Financial Disclosure Documentation
5844 - Europe	Completed prior to February 2, 1999 (November 1997)	Appropriate documentation; no financial arrangements/proprietary interest
6793 – U.S.	Ongoing as of February 2, 1999 (two patients remain on study)	Appropriate documentation; no financial arrangements/proprietary interest
6410 - Australia	Completed prior to February 2, 1999	Appropriate documentation; no financial arrangements/proprietary interest

Conclusion:

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54.

Attachment A

U.S. Investigator List
Financial Certification

Investigator/Center Number	Country
Study 6793:	
B. D. Anawalt, M.D./03	U.S.
S. Bhasin, M.D./01	U.S.
P. Boepple, M.D./02	U.S.
W. F. Crowley, M.D./02	U.S.
J. E. Hall, M.D./02	U.S.
F. Hayes, M.D./02	U.S.
K. A. Martin, M.D./02	U.S.
A. Matsumoto, M.D./03	U.S.
P. J. Snyder, M.D./09	U.S.
D. Spratt, M.D./04	U.S.
T. J. Weber, M.D./07	U.S.
C. Welt, M.D./02	U.S.
S. Winters, M.D./06	U.S.

Attachment B

Non - U.S. Investigator List
Financial Certification

Investigator/Center Number	Country
Study 5844:	
P. M. Bouloux, M.D./01	United Kingdom
C. Cortet-Rudelli, M.D./04	France
Prof. D. DeWailly, M.D./04	France
T. H. Jones, M.D./02	United Kingdom
Prof. W. Krause, M.D./06	Germany
H. Lejeune, M.D./03	France
Prof. M. Pugeat, M.D./03	France
R. Quinton, M.D./01	United Kingdom
Prof. G. Schaison, M.D./05	France
Prof. A. P. Weetman, M.D./02	United Kingdom
J. Young, M.D./05	France
Study 6410:	
H. W. Gordan Baker, M.D/02	Australia
A. Conway, M.D./01	Australia
Prof. D. J. Handelsman, M.D./01	Australia
R. McLachlan, M.D./02	Australia
W. Watkins, M.D./02	Australia

Attachment C

List of Investigators
for whom Due Diligence was Performed but Disclosure was not Obtainable

Investigator/Center Number	Country	Reason Information Not Obtained
Study 6793:		
K. Bachus, M.D./07	U.S.	No forwarding address
N. Bossert, M.D./07	U.S.	No forwarding address
R. V. Clark, M.D./07	U.S.	No forwarding address

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Serono Laboratories, Inc.

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

APR 28 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
ODE III
Division of Reproductive and Urologic Drug Products

Date: April 28, 2000

From: Mark S. Hirsch, M.D., Acting Urology Medical Team Leader, HFD-580

Subject: NDA 20-378, Supplement 006
Gonal-F™ (recombinant human follicle stimulating hormone) for the induction of spermatogenesis in men with primary and secondary hypogonadotrophic hypogonadism and in whom the cause of infertility is not due to primary testicular failure.

To: Susan Allen, M.D., Acting Division Director, HFD-580

The purpose of this memo is to provide the Acting Division Director with the medical team leader's recommendation regarding this supplemental NDA. Briefly, the acting medical team leader believes that this supplemental NDA should be approved. This recommendation is based on the data submitted in the application, which provides clear and substantial evidence demonstrating that the product is safe and effective for the proposed new indication.

Gonal-F, or recombinant FSH, is an approved drug product which is currently indicated for ovulation induction in oligo-anovulatory infertile women and for the development of multiple follicles in women participating in an assisted reproductive techniques program.

The sponsor conducted an investigative program, specifically designed to assess whether Gonal-F was effective in the induction of spermatogenesis in men with hypogonadotropic hypogonadism and azoospermia, in whom infertility was not due to primary testicular failure. The program consisted of 3 separate trials. Trial 6793 was conducted at 7 United States centers and enrolled 30 patients. Trial 5844 was conducted at 6 European centers and enrolled 32 patients. Finally, Trial 6410 was conducted at 2 Australian centers and enrolled 10 patients.

The designs of these 3 trials were similar. The medical officer's review details the minor differences in dose and exclusion criteria. It is the opinion of the acting team leader that these differences do not substantially impact on the ultimate approvability of the product or safe and effective use of the product. The studies were open-label in design. Essentially, all patients meeting the entry criteria received "pre-treatment", using daily subcutaneous injections of human chorionic gonadotropin (Profassi), for 3 to 6 months in order to bring the serum testosterone (T) levels into the normal range. The doses of Profassi were individualized to best suit the needs of individual patients. Those patients who remained azoospermic after successful normalization of their serum T levels, were continued on Profassi but also begun on Gonal-F. Gonal-F was continued for up to 18 months with intermittent monitoring of semen parameters. Again, the dose of Gonal-F could be increased from 150 IU daily (subcutaneous administration) up to 300 IU daily based on the patient's individual response.

The pre-defined primary endpoint for all the trials was the proportion of patients who achieved a sperm concentration of 1.5 million sperm per milliliter of semen. Secondary endpoints included the mean sperm concentration, the percentage of normal sperm forms, the percentage of sperm with forward progressive motility, the mean total sperm per ejaculate and the actual number of pregnancies and live births.

The efficacy results demonstrated that the combined use of Profasi and Gonal-F was effective in the induction of spermatogenesis in these patients. Of the 72 enrolled patients, 56 actually received Gonal-F. The sponsor clearly documented the reasons for some enrolled patients not receiving Gonal-F. These reasons included such issues as inability to normalize the serum T level during pre-treatment, achievement of sperm in the ejaculate during pre-treatment, withdrawal for personal reasons and protocol violations. In the three trials, 64%, 46% and 63% of patients who received Gonal-F, respectively, met the primary endpoint. The secondary endpoints were supportive of efficacy. Specifically, the mean sperm concentrations were 14.8 million/ml, 16.2 million/ml and 8.5 million/ml, respectively. The mean total sperm per ejaculate were 46.8 million, 32.5 million, and 25.8 million, respectively. Normal forms of sperm and progressive motility were similarly improved. Finally, of most importance, there were three pregnancies achieved in Trial 6793, six pregnancies achieved in Trial 5844 and three pregnancies in Trial 6410. These 12 pregnancies (in 10 partners) resulted in the births of eight healthy babies. Thus, of the 37 patients seeking children in the combined trials, 10 patients (or 27%) were successful in this objective.

The safety results demonstrated no deaths and only one serious adverse event; a single patient required partial mastectomy for development of benign gynecomastia. In this patient, gynecomastia had developed previously with prior androgen therapy, was again noted during the pretreatment phase of the trial, but surgery was carried out only after treatment with Gonal-F. Overall drug-related adverse events were generally mild to moderate in severity, and may have been related to treatment with hCG alone. These events included acne, gynecomastia, breast discomfort, and testicular pain. There were very rare reports of severe injection site reaction, consisting primarily of pain.

There is only one major question which impacts on the approval decision. That is: could Profasi alone have provided similar results? The reviewers do not believe so. There is solid evidence from the literature (see the medical officer's review) that in men with hypogonadatropic hypogonadism *and small testicles* (particularly < 4 ml in volume), the effect of hCG alone is negligible and does not result in induction of spermatogenesis. The sponsor was careful to enroll men with small testicles into these trials. In Trial 5844, men with testes > 4 ml were excluded. In Trial 6793, men with testes > 6 ml were excluded. In Trial 6410, testicular volume was not an entry criterion, however, the average testicular volume was only 4.5 ml.

It might be argued that these trials did not control for placebo effect. Again, based on solid evidence from the literature and long-standing clinical opinion, the reviewers are convinced that placebo treatment would not have resulted in induction of spermatogenesis in these patients.

It also could be argued that 1.5 million sperm per milliliter of semen is a relatively modest concentration. Again, evidence from the literature, as well as clinical evidence from these trials, demonstrates that even such modest improvement may be sufficient to allow these patients to achieve pregnancy.

Finally, there is a single outstanding issue and that is a question of the dose of Profasi used in the trials. In the United States centers, Profasi was administered in *USP units*, while the remainder

of the international centers administered Profassi as *IU*, or *International Units*. While this variation in the use of Profassi should be standardized in the American package insert (labeling revision in progress), the reviewers do not believe that such minor differences in units of activity (an approximate 8% increase in biologic activity of hCG in the United States centers compared with the other centers) had a clinically meaningful impact on the actual efficacy results. This is particularly true because the dose of Profassi was individualized per patient to simply allow for normalization of the serum T levels.

Therefore, based upon our acceptance of the study designs as appropriate, the ultimate resolution of the Profassi dose in the American package insert, and the acknowledgement of clear patient benefit in the face of minimal risk, I recommend that this supplemental NDA should be approved.

/S/

Mark S. Hirsch, MD
Acting Urology Medical Team Leader, HFD-580
Division of Reproductive and Urologic Drug Products.

4/28/00

cc: Arch NDA 20-378
HFD-580/Div File
HFD-580/SAllen/MMann/DShames/GBenson/FDeGuia

APR 28 2000

NDA 20378 – supplement S-006

Date supplement submitted: July 26, 1999
Date supplement received: July 27, 1999
Review completed: April 19, 2000
Revisions completed: April 26, 2000

Medical Officer Review

Sponsor:	Serono Laboratories, Inc. 100 Longwater Circle Norwell, MA 02061
Drug:	Generic: follitropin alpha (recombinant human follicle stimulating hormone) Trade: Gonal-F Chemical: recombinant human follicle stimulating hormone (FSH)
Route:	Subcutaneous injection
Dosage form:	Lyophilized drug in single dose ampules
Strength:	Ampules containing either 75 IU or 150 IU
Proposed indication:	Induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism and in whom the cause of infertility is not due to primary testicular failure.
Related INDs:	38,712 43,865
Other regulatory action:	On December 21, 1998, Serono received approval for orphan drug designation subject to final submission and approval of this supplemental NDA. [5]

TABLE OF CONTENTS

1.0 Resume: In support of the safety and efficacy of Gonal-F in combination with human chorionic gonadotrophin (hCG) in inducing spermatogenesis in men with hypogonadotrophic hypogonadism (HH), the sponsor submitted the results of 3 clinical trials:

- Trial 6793, a multicenter, non-comparative study conducted at 7 centers in the United States. Of 30 patients enrolled in this study, 22 received Gonal-F prior to the cut-off date for interim analysis specified in Amendment 4.

- Trial 5844, a multicenter, non-comparative study conducted at 6 centers in France, the United Kingdom, and Germany. Of 32 patients enrolled in this study, 26 received Gonal-F.

- Trial 6410, a dual-center, non-comparative study conducted at 2 centers in Australia. Of 10 patients enrolled in this study, 8 received Gonal-F.

The design of the three studies was similar. All patients had a diagnosis of primary or secondary hypogonadotrophic hypogonadism (HH) based on clinical and hormonal evaluation and all had azoospermia. Following a drug "washout" period following discontinuation of testosterone or hCG therapy, patients were given hCG for a 3 to 6 month period until serum testosterone had normalized. If they remained azoospermic at the end of this "pretreatment" phase, they were then treated with Gonal-F for 18 months. The primary endpoint in all 3 studies was the proportion of patients who achieved a spermatozoa concentration of $> 1.5 \times 10^6$/ml. of semen. Secondary endpoints included 1) spermatozoa count per ejaculate and per ml 2) mean testis volume 3) serum inhibin concentrations 4) percentage of spermatozoa with normal morphology 5) percentage of spermatozoa with progressive motility and 6) pregnancy in partners during therapy for couples desiring fertility.

There were several differences between study designs for the 3 trials:

1) Dose of hCG and Gonal-F (Table 1)

Table 1. Doses of hCG and Gonal-F in each trial.

	Trial 6793	Trial 5844	Trial 6410
Dose hCG	1000 U q 2 days	2000 U 2x/week	2000 U 2x/week
Dose Gonal-F	150 IU q 2 days	150 IU 3x/week	150 IU 2x/week

2) Exclusion criterion for testicular size:
Trial 6793: mean testicular volume >6 ml excluded
Trial 5844: mean testicular volume > 4ml excluded
Trial 6410: no testicular size exclusion

3) Trial 5844 excluded patients who had received prior GnRH or FSH therapy while Trials 6793 and 6410 did not.

None of the 3 trials were placebo controlled and none included a comparator arm. Spontaneous resolution of this disorder is extremely rare. In view of the rarity of this disorder, the stable nature of the deficiency, and the objective efficacy measures employed in this study, the sponsor suggested that a non-comparative study design was acceptable. In addition, the use of a placebo control was considered unethical for the prolonged duration of exposure that such a study would entail. The use of a comparator treatment group would also have significantly reduced the number of evaluable patients with this rare disorder in the study drug arm. The reviewer agrees that the study design is acceptable.

Prior studies have demonstrated that hCG alone can induce spermatogenesis in men with HH.[1] In the referenced study, while a large proportion of men with larger initial testicular volume produced sperm with hCG alone, very few men with smaller testes were successful. In the latter group with smaller testicles, all men who produced sperm achieved counts of $<1 \times 10^6$/ml. Other published data support the concept that the most important factor in determining spermatogenic responsiveness to hCG alone is pretreatment testicular volume.[2] In the study of Kung, all patients who responded to hCG alone had an initial testicular volume of > 4 ml. In Trial 6793 patients with testicular volume >6 ml were excluded and in Trial 5844 the testicular volume exclusion criterion was >4 ml.

Efficacy: The proportion of patients achieving the primary endpoint ($> 1.5 \times 10^6$ spermatozoa/ml) is shown in the following table (Table 2):

Table 2. Proportion of patients who received Gonal-F who achieved $>1.5 \times 10^6$ spermatozoa/ml

Trial 6793	Trial 5844	Trial 6410
63.6%	46.2%	62.5%

Although the primary endpoint appears to be only a modest increase in sperm concentration, such a sperm concentration ($>1.5 \times 10^6$/ml) has been reported to allow 92% of men with HH treated with hCG and menotropins to achieve pregnancy. In addition, the mean total sperm counts and mean sperm concentrations were substantially greater than 1.5×10^6 spermatozoa/ml.

Secondary endpoints were supportive of drug efficacy (Table 3).

[1] Burris AS, Rodbard HW, Winters SJ, Sherins RJ. 1988 Gonadotrophin therapy in men with isolated hypogonadotropic hypogonadism: The response to human chorionic gonadotropin is predicted by initial testicular size. J Clin Endocrinol Metab. 66: 1144-1151.

[2] Kung AWC, Zhong YY, Lam KSL, Wang C. 1994. Induction of spermatogenesis with gonadotrophins in Chinese men with hypogonadotrophic hypogonadism. Int J Androl. 241-247.

Table 3. Secondary endpoints in patients who received Gonal-F

	Trial 6793 (N=22)	Trial 5844 (N=26)	Trial 6410 (N=8)
Mean testicular volume (ml)			
End pretreatment	7.1	2.5	5.6
Month 18	16.8	12.2	9.6
Mean total sperm count (x 10^6)			
End pretreatment	0.0	0.0	0.0
Month 18	46.8	32.5	25.8
Mean sperm concentration (x 10^6/ml)			
End pretreatment	0.0	0.0	0.0
Month 18	14.8	16.2	8.5

Three pregnancies were achieved in Trial 6793, six in Trial 5844, and three in Trial 6410. These pregnancies resulted in the births of 8 healthy children and 4 miscarriages.

Safety: There were no deaths or serious adverse events related to study drug. Two of the most frequently reported adverse events (acne and gynecomastia) are known side effects of androgen therapy. Testicular pain reported in Trial 6793 and varicoceles reported in Trial 5844 may also be secondary to androgen therapy. The hematologic and chemistry changes (hematocrit and creatinine elevations over baseline but still within normal limits) are also known effects of androgen therapy.

In summary, the reviewer believes that Gonal-F is safe and effective therapy for the induction of spermatogenesis in men with HH.

2.0 Background

2.1 Regulatory History: In 1993 Serono submitted NDA # 20-378 for Gonal-F for the female indications of ovulation induction in oligo-anovulatory infertile women and for induction of multiple follicular development in women participating in an ART program. Marketing approval for these indications was granted on September 29, 1997. In November, 1993, Serono submitted IND # 43,865 for Gonal-F for male indications. In October, 1998, Serono applied for orphan designation for Gonal-F when used for the current proposed indication for induction of spermatogenesis in men with HH. In December, 1998, Serono received approval for orphan designation subject to final submission and approval of the supplemental NDA.

2.2 Clinical Background and Scientific Rationale: HH is a rare disorder (incidence of approximately 1 in 10,000) of reproductive function which occurs in both men and women. The primary pathophysiology is the absence of effective hypothalamic-pituitary release of gonadotropins resulting in arrested or attenuated gonadal function. In men, the disorder may present as failure to undergo physical changes associated with puberty or, if

it occurs after puberty, may present as regression of secondary sexual characteristics, loss of libido, or impotence. In addition, lack of testicular stimulation by gonadotrophins leads to infertility.

HH can be subdivided into primary and secondary causes. Primary HH includes congenital absence of functional gonadotropin hormone-releasing hormone (GnRH) secreting neurons, a condition referred to as idiopathic hypogonadotropic hypogonadism (IHH). IHH may be associated with mid-line fusion defects, a syndrome also referred to as septo-optic dysplasia. When anosmia is associated with IHH, the disorder is referred to as *Kallmann's syndrome*. IHH may also be found in association with Prader-Willi and Laurence-Moon-Biedl syndromes. In some of these disorders, particularly when associated with structural mid-line lesions, IHH may be associated with growth hormone deficiency. Secondary causes of HH include hypothalamic tumors (hamartoma and craniopharyngioma), pituitary ischemia (Sheehan's syndrome), and pituitary lesions (acromegaly, Cushing's disease, and prolactinoma).

The diagnosis of HH is established by history, physical examination, and the demonstration of low serum testosterone in the presence of low serum LH and FSH levels. Additional confirmation and localization of the defect may be provided by endocrine stimulation studies and radiologic imaging studies.

Treatment of men with HH requires addressing both testicular steroidogenesis and spermatogenesis. In patients not seeking fertility, androgen replacement (with either testosterone or hCG) is sufficient therapy. Fertility, however, requires initiation or re-initiation of spermatogenesis. Men with HH may not require spermatogenesis to reach the normal adult range for pregnancy to be achieved. A sperm density of $>1 \times 10^6$/ml has been reported to permit pregnancy in 92% of partners of HH men treated with hCG and menotropins.[3]

Induction of spermatogenesis requires the replacement of both LH and FSH, particularly in men with low pre-treatment testicular volume. hMG (which contains equal quantities of LH and FSH) is commonly used as a source of FSH. In the absence of an effective therapeutic preparation of LH, hCG is indicated for stimulation of androgen production by the testis. hMG has remained the standard source of FSH for the induction of spermatogenesis. hMG administered with hCG is currently approved for initiation or re-initiation of spermatogenesis in men with HH.

Currently FSH is approved in combination with LH for treatment of men with HH. The approved form is extracted from urinary sources such as hMG. Gonal-F is a recombinant human FSH produced from genetically engineered Chinese Hamster Ovary cells cultured in bioreactors.

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[3] Burris AS, Clark RV, Vantman DJ, Sherins RJ. A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. Fertil Steril 1988; 50:343-347.

2.3 International Marketing Experience: In June, 1999, Serono received approval from the European Medicines Evaluations Agency (EMEA) to market Gonal-F for the treatment of male HH. Gonal-F was also approved in December, 1996, for the treatment of male HH in Argentina. No post marketing data from Europe or Argentina is available to the reviewer.

3.0 Summary of NDA Clinical Section: In support of the proposed indication, the sponsor conducted 3 clinical trials. These 3 trials form the basis of this review and no other efficacy or safety data was analyzed.

- Trial 6793: a multicenter, non-comparative study performed at 7 centers in the United States (30 patients enrolled)
- Trial 5844: a multicenter, non-comparative study performed at 6 centers in Europe (32 patients enrolled)
- Trial 6410: a 2 center, non-comparative study performed in Australia (10 patients enrolled)

The results of these 3 trials are discussed in sections 4.0, 5.0, and 6.0.

4.0 Clinical trial **GF 6793**: ("A Phase 3, Multicenter, Non-comparative Study to Assess the Safety and Efficacy of Recombinant Human Follicle Stimulating Hormone (Gonal-F) in Combination with Human Chorionic Gonadotrophin (hCG) in Inducing Spermatogenesis in Men with Hypogonadotropic Hypogonadism") The study began in October, 1994, and ended on the interim analysis report date of March 11, 1998.

4.1 Objectives: The study objective is to determine the safety and efficacy of Gonal-F in inducing spermatogenesis in azoospermic men with hypogonadotropic hypogonadism (HH).

4.2 Design and Conduct Summary: This protocol is a multicenter (7 United States sites), non-randomized, non-controlled, non-comparative, open label, escalating dose study to assess the safety and efficacy of recombinant human follicle-stimulating hormone (r-hFSH, Gonal-F) administered subcutaneously in combination with human chorionic gonadotrophin (hCG, Profasi) given intramuscularly or subcutaneously to induce spermatogenesis in men with HH. Thirty men (aged 17 to 55) with HH and azoospermia were enrolled. The screening evaluation included medical and medication history, physical examination, measurement of testis volume using a Prader orchidometer, and laboratory screening including serum LH, FSH, prolactin, testosterone (T), TSH, cortisol, estradiol (E_2), hematology, chemistry, urinalysis, and semen analysis. Patients were then entered into the "pre-treatment" phase of the study and received 1000 U Profasi (hCG) IM or SC every other day for at least 3 months. After 2 months of Profasi treatment, Serum T, hCG, and E_2 were determined. If necessary, Profasi dosing could be modified during the third month to maintain T levels within the normal range. If T levels had not normalized within 3 months, the Profasi dose was adjusted by no more than 50%, and serum T levels were measured monthly until normal levels were achieved. Two

consecutive months of normal T concentrations were necessary for the patient to continue on to the study treatment phase. Patients who were unable to produce a semen sample to continued Profasi monotherapy for an additional 3 months. The total Profasi pre-treatment phase was not to exceed six months.

Prior to entering the treatment phase, all patients were required to have a repeat semen analysis which showed azoospermia. In addition, patients underwent a physical examination (including testes volume) and laboratory evaluation which included hematology, chemistry, urinalysis, and serum T, hCG, and E_2. Measurement of FSH, inhibin, and determination of antibodies to Gonal-F were to be assayed retrospectively. During the treatment phase, Gonal-F was administered SC at a dose of 150 IU every other day in combination with Profasi (IM or SC) at a dosage of 1,000 U USP, or the dose of Profasi needed to maintain the T level in the normal range as determined during the pretreatment phase, for 18 consecutive months. During the treatment phase, the dose of Gonal-F was to be increased by 75 IU if the patient were still azoospermic at the end of 6 months of treatment. A further 75 IU increase was permitted if the patient were still azoospermic at the end of 12 months of treatment or if there were not an increase of at least 20% in sperm count compared to the 6 month level. Thus, the maximum dose of Gonal-F could have been 300 IU every other day during the last 6 months of the treatment phase. The same assessments conducted during the pretreatment phase were conducted at regular intervals during the treatment phase including determination of testis volume and sexual characteristics, serum T, hCG, and E_2, as well as FSH, inhibin, and semen analyses at months 3, 6, 9, 12, 15, and 18. Other laboratory tests including hematology, chemistry, urinalysis, and measurement of antibodies to Gonal-F were performed at months 3, 12, and 18. Finally, local tolerance to study drug was assessed following each injection by the patient and an injection diary was maintained by the patient.

Reviewer's comments: The starting dose of hCG was 1000 U every 2 days compared to 2000 U 2 times per week in trials 5844 and 6410. The starting dose of Gonal-F was 150 IU every two days compared to 150 IU 3 times per week in trial 5844 and 150 IU 2 times per week in trial 6410. These minor dose variations are not clinically significant.

4.3 Study population: The study population was men with HH defined as patients with serum T levels < 100 ng/ml and low or normal FSH and LH. Patients were required to have had a "washout period" for other medication used to treat HH prior to enrollment and treatment. Patients with major medical illnesses were excluded; however, patients with associated endocrine states were not excluded. The median age of the 30 patients was 29.5 years (age range: 22-44 years). The median age at which the 30 patients were diagnosed with HH was 18 years (range 8-35 years). Ten of the 30 patients were anosmic and therefore diagnosed with Kallmann's syndrome.

4.4 Inclusion and exclusion criteria: Inclusion criteria included men aged 17 to 55. If the patient were under 21 years of age, bone age had to be at least 15 years and/or he must have been confirmed to have anosmia. No T or hCG replacement therapy was allowed for at least 8 weeks prior to the pre-study assessment. Within 2 months prior to the pre-study

assessment, the following hormonal criteria were required: 1) LH: low or normal 2) FSH: low or normal 3) prolactin: <25 ng/ml 4) T: <100 ng/dl 5) TSH:>0.5 and <5.5 mIU/ml and 6) cortisol: within the normal range. If the serum TSH were below the normal range, a free T4 determination was required. If the T4 were normal, the patient was eligible for the study. All patients were required to 1) be azoospermic as shown by a semen analysis performed within 2 months prior to entry into the pretreatment phase 2) have a mean testis volume of <6 ml 3) have no active pituitary or hypothalamic mass or lesion and 4) have a body mass index not greater than 30.9 (later amended to 34.9). Exclusion criteria included any disease which might interfere with the results of the study or modify the condition under study such as diabetes mellitus, cardiomyopathy, hepatic or renal disease, hemochromatosis, Cushing's syndrome or hyperthyroidism. Other exclusion criteria included: 1) medical records documenting a serum T level >100 ng/dl and/or serum FSH and LH concentrations above the normal range at the time of initial HH diagnosis 2) if previously treated with hCG, had required a dose of more than 10,000 U USP per week to normalize serum T concentrations 3) any past or current condition which could lead to testicular dysfunction (testicular torsion or cryptorchidism) 4) any past or current condition which could lead to obstruction of the vas deferens and 5) grade 3 or 4 varicocele.

Reviewer's comments: It should be noted that prior GnRH or FSH therapy was allowed in this study and in trial 6410, but was excluded in Trial 5844. In this study a testicular volume of > 6 ml was an exclusion criterion. In Trial 5844 the testicular size exclusion criterion was >4 ml and Trial 6410 did not consider testicular size as an exclusion criterion.

4.5 Primary and secondary endpoints: The primary endpoint was the proportion of patients who achieved a spermatozoa concentration of >1.5 x 10^6/ml. Secondary endpoints included: 1) mean testis volume, 2) serum inhibin concentrations, 3) spermatozoa count per ejaculate and per ml, 4) percentage of spermatozoa with normal morphology, 5) percentage of spermatozoa with progressive motility, 6) ejaculate volume, and 6) pregnancy in partners during therapy for couples desiring fertility.

Reviewer's comment: The primary endpoint is the induction of a low sperm concentration. In patients with HH, fertility has been reported to occur with relatively low sperm densities.[3]

4.6 Withdrawals, compliance, and protocol violations: 30 patients were enrolled into the study and received at least 1 dose of Profasi in the pretreatment phase. **After the March 11, 1998, cutoff date, no further data were included in this interim analysis of this ongoing trial.** (Amendment 4 submitted to the IND on November 4, 1998, set a cut-off date for data to be included in the interim analysis of March 11, 1998.) Twenty-three patients completed the Profasi pretreatment phase. Of the 7 remaining patients, 4 are still in the pretreatment phase as of the March 11, 1998, cutoff date. Three patients were discontinued. Of the three, two had measurable sperm counts following 5.3 and 3.7 months of Profasi treatment. The third patient was discontinued due to his inability to achieve a normal testosterone level and to produce a semen sample for verification of

azoospermia. Of the 23 patients who completed the pretreatment phase, 22 entered the treatment phase. The remaining patient withdrew for personal reasons. Of the 22 patients who entered the treatment phase, 10 completed therapy, 9 are still receiving therapy as of the March 11, 1998, cut-off date, and 3 patients were discontinued. The reasons for the 3 discontinuations were: 1) protocol violation following voluntary admission to a drug rehabilitation center for the treatment of substance abuse 2) adverse event consisting of complaints of "tiredness, dizziness, and sweats." Follow-up examination of this patient revealed hepatitis B (positive hepatitis B core antibody) and 3) personal reasons (relocation abroad).

Three patient populations were analyzed in the efficacy analysis:

1) The completed treatment population (10 patients) which consisted of patients who completed 18 months of Gonal-F treatment.
2) The completed protocol population (13 patients) which consisted of patients who completed 18 months of Gonal-F treatment or who withdrew prematurely from the study in accordance with protocol directives.
3) The population of patients who received at least one dose of Gonal-F (22 patients).

Safety data were derived from the "safety population" consisting of all patients who were enrolled in the study and received at least one dose of Profasi in the pretreatment phase.

Protocol violations: Five of the 30 patients did not satisfy all of the eligibility requirements for entry into the study. Patient #010003 had an MRI performed after approximately 1 month of Profasi treatment in the pretreatment phase (as opposed to having the study performed in the pre-study phase.) The MRI showed a "congenital cyst." Patient #030008 had a history of cryptorchidism, a testicular volume of 6.5 ml, and a questionable pituitary microadenoma. An independent reviewer's reading of the MRI concluded that there was no significant pathology. Patient # 090002 had a prestudy cortisol level of 25 ug/dl (top normal is 24 ug/dl) and Patient #090004 had a cortisol level of 7 ug/dl (low normal limit is 8 ug/dl). The fifth patient (#040001) had a prestudy BMI of 32.6 kg/m^2. In addition to these 5 patients, Patient #020002 had a distant history of recreational cocaine and marijuana use. Five patients exceeded the scheduled 18 month duration of therapy with Gonal-F. In those 5 patients, therapy ranged from 18.5 to 22.0 months. Gonal-F dose escalations were employed for 3 patients who were not azoospermic at the time of dose adjustments. The sponsor believes that none of the protocol violations were major and did not impact the safety and efficacy analyses and the reviewer agrees.

4.7 Efficacy analysis: The primary endpoint was the proportion of patients who achieved a spermatozoa concentration of $>1.5 \times 10^6$/ml. These results are shown in Table 4. For analysis purposes, 3 patient groups were identified:

1) The "completed treatment group" consisted of 10 patients who completed 18 months of Gonal-F treatment and were evaluable for the primary endpoint at the time of data cutoff.
2) The "completed protocol group" consisted of 13 patients who either completed the 18 month treatment period or were discontinued for reasons defined in the protocol.

(This group includes the 10 patients in the completed treatment group plus 3 patients who were discontinued.)

3) The "intent to treat group" consisted of 22 patients who received at least one dose of Gonal-F. (This group includes the 13 patients in the completed protocol group plus 9 patients who were continuing Gonal-F treatment at the time of data cutoff.)

Table 4. Patients who achieved spermatozoa concentrations >1.5 x 10^6/ml in the 3 efficacy populations.

	Completed Treatment (N=10)	Completed Protocol (N=13)	Intent to Treat (N=22)
>1.5 x 10^6/ml sperm	9 (90%)	11 (84.6%)	14 (63.6%)

Those secondary endpoints which in the reviewer's opinion are the most clinically relevant are presented below:

Table 5. Sperm concentration (x 10^6/ml) at last available assessment (three efficacy populations)

	Completed Treatment (N=10)	Completed Protocol (N=13)	Intent to Treat (N=22)
Mean (SE)	14.8 (6.7)	14.0 (5.3)	10.6 (3.4)
Median	5.8	6.0	5.4
Range			
p-value (compared to baseline)	<0.001	<0.001	<0.001

Table 6. Total sperm count per ejaculate (x 10^6) at last available assessment, three efficacy populations.

	Completed Treatment (N=10)	Completed Protocol (N=13)	Intent to Treat (N=22)
Mean (SE)	46.8 (27.9)	38.2 (21.7)	27.9 (13.4)
Median	15.5	14.7	10.3
p-value (compared to baseline)	<0.001	<0.001	<0.001

Table 7. Semen analysis: normal morphology (%) at last available assessment, three efficacy populations.

	Completed Treatment (N=10)	Completed Protocol (N=13)	Intent to Treat (N=22)
N	10	12	16
Mean (SE)	24.1 (8.1)	21.3 (6.9)	19.9 (5.4)
Median	13.0	11.0	11.0
Range			
p-value (compared to baseline)	0.002	<0.001	<0.001

Table 8. Semen analysis: progressive motility (%) at last available assessment, three efficacy populations.

	Completed Treatment (N=10)	Completed Protocol (N=13)	Intent to Treat (N=22)
N	10	12	18
Mean (SE)	39.8 (5.6)	40.7 (5.0)	41.2 (6.4)
Median	37.0	37.0	37.0
Range			
p-value (compared to baseline)	<0.001	<0.001	<0.001

Table 9. Mean testis volume (ml), changes within pretreatment and treatment phases, three efficacy populations.

		Completed treatment (N=10)	Completed protocol (N=13)	Intent to Treat (N=22)
Prestudy to end of pretreatment	Mean (SE)	2.5 (1.0)	2.5 (0.8)	2.7 (0.6)
	Median	1.0	1.0	1.5
End of pretreatment to end of treatment	Mean (SE)	10.0 (1.5)	8.4 (1.5)	6.5 (1.1)
	Median	8.5	8.5	6.1

Other secondary endpoints:

Pregnancy: At the time of study entry, 24 of the 30 patients desired fertility as an outcome of study treatment. Two clinical pregnancies and one "biochemical" pregnancy occurred in partners of study patients prior to data cutoff:

1) The partner of Patient 010001 became pregnant approximately 14 months after Gonal-F therapy was initiated. Ultrasound at 19 weeks gestation revealed a single

fetal sac. At the month 12 visit, the patient's sperm concentration was 4.2 x 10^6/ml. A healthy 6 pound 5 ounce baby boy was born.

2) A single fetal sac with fetal heart activity was detected by ultrasound in the partner of Patient 070001 after the patient had completed the study. The pregnancy, however, resulted in a spontaneous abortion. The patient's Month 15 and 18 sperm concentrations were 12.5 and 5.1 x 10^6/ml.
3) The results of a biochemical pregnancy test were positive for the partner of Patient 030003 during his eighteenth month of Gonal-F treatment. An ultrasound one week later, however, did not confirm a fetal sac or heart activity. The pregnancy outcome was considered to be a preclinical spontaneous abortion. The patient's Month 15 and 18 sperm concentrations were 25 and 25 x 10^6/ml.

No inhibin data were available at the time of the study cut-off date.

4.8 Safety Analysis

4.8.1 Extent of exposure: The extent of Profasi and Gonal-F exposure is depicted in Table 10.

Table 10. Summary of Administered Doses: Gonal-F and Profasi during the treatment phase: all patients who received at least one dose of Gonal-F (N=22)

Total number of treatment FSH injections (mean)	197.0
Total number of treatment hCG injections (mean)	197.5
Total number of treatment injections (mean)	394.5
Total amount (IU) of treatment FSH injected (mean)	32,833.0
Total amount (U) of treatment hCG injected mean)	211,222.7

4.8.2. Serious adverse events: There were no study deaths. Three serious adverse were reported. One serious adverse event was reported during the pretreatment phase. Patient #040002 required hospitalization for a fractured right humerus. This event was judged to be unrelated to Profasi treatment. Two serious adverse events were reported (both in Patient #020002) during the treatment phase. The events consisted of depression and drug abuse, both requiring hospitalization. Both events were rated as moderate in severity and were considered of remote relationship to the study drug.

Reviewer's comment: The reviewer agrees that the adverse event in Patient #040002 is unrelated to study drug and that the two adverse events in Patient #020002 are unlikely to be related to study drug.

4.8.3 Discontinuation due to adverse events: One patient, #020003, withdrew from the treatment phase prior to completing the study due to an adverse event consisting of "tiredness, dizziness, and sweats." The patient was subsequently found to have hepatitis B (positive hepatitis B core antibody).

4.8.4 Frequent adverse events: A total of 127 adverse events were reported during the pretreatment and treatment phases of the study. During the pretreatment phase, 14 of the 30 patients (46.7%) reported a total of 28 adverse events, while 18 of the 22 patients (81.8%) reported a total of 99 adverse events during the treatment phase. 78% of all adverse events were reported during the treatment phase.

Pretreatment phase: The adverse events reported by >5% of patients were:

Table 11. Adverse events reported by >5% of patients in the pretreatment phase.

Acne	13.3%
Testicular pain	13.3%
Gynecomastia	6.7%
Allergy	6.7%

Treatment phase: Adverse events reported by >5% of patients were:

Table 12. Adverse events reported by >5% of patients in the treatment phase.

Acne	50.0%
Fatigue	27.3%
Pain	13.6%
Back pain	13.6%
Flu-like symptoms	13.6%
Breast pain	13.6%
Diarrhea	9.1%
Sinusitis	9.1%
Rhinitis	9.1%
Somnolence	9.1%
Gynecomastia	9.1%
Heart murmur	9.1%
Injection site pain	9.1%

Reviewer's comment: Some of the adverse events (acne and gynecomastia) are recognized side effects of androgen therapy. The association of these adverse events with Gonal-F is uncertain.

During the treatment phase, 3 patients had adverse events which were considered severe. One patient experienced acne, one abdominal pain, and one injection site pain.

88.4% of 4,334 Gonal-F injections were associated with either no reaction or mild pain. 2.8% of the injections were associated with severe pain.

4.8.5 Changes in laboratory values: None of the minimal shifts seen in hematologic parameters was considered by the investigators to be clinically significant. Seven chemistry results (2.5% of abnormal results and 0.2% of all results) were considered to be

clinically significant by the investigators. Two patients had elevated alkaline phosphatase levels. One (#030008) patient had an elevated alkaline phosphatase level to 150 IU/L (normal range 39-117 IU/L) at the end of pretreatment which was preceded 4 days earlier by the patient experiencing mid-back pain following an automobile accident. During the treatment phase, alkaline phosphatase levels were 171 and 178 IU/L. The Month 12 results were not obtained at the time of the data cutoff. The investigator determined this elevation to be of remote relationship to the study drug. Another patient (#020001) had an elevation of alkaline phosphatase to 315 IU/L which the investigator attributed to a knee injury. The alkaline phosphatase level normalized at Month 18 and was judged by the investigator to be unrelated to study drug. One patient (#010003) had an elevated uric acid level of 7.9 mg/dL at the final 18 month visit. His uric acid levels were mildly elevated at the end of pretreatment and at month 3 of treatment. The investigator thought that the hyperuricemia was unrelated to study drug. At Month 18, Patient #010004 had an elevated total bilirubin of 1.5 mg/dL. At pre-study and at the end of pre-treatment, bilirubin levels were normal. The investigator rated this event as of unknown relationship to the study drug. At the end of pre-treatment, Patient #020003 had slightly elevated levels of ALT and AST. His liver enzymes began to fall, and he was found to be infected with hepatitis B. The final patient (#060001) had a mildly elevated blood glucose which was thought to be unrelated to study drug.

The results of antibodies to Gonal-F were not reported by the study cut-off date.

4.9 Reviewer's assessment of safety and efficacy in Trial 6793:

This trial does not include either a control group or a comparator arm. However, spontaneous resolution of HH is extremely rare. In view of the rarity of this disorder, the stable nature of the deficiency, and the objective efficacy measures employed in this study, the sponsor suggests that a non-comparative study design is acceptable. In addition, the use of a placebo control was considered unethical for the prolonged duration of exposure such a design would entail. The use of a comparator treatment group would have significantly reduced the number of evaluable patients with this rare disease in the study drug arm. The reviewer believes that the study design is acceptable.

HH is a disorder of both steroidogenesis and spermatogenesis. hCG alone (2000 U administered 3 times/week) has been reported to induce spermatogenesis in men with HH. Other data have demonstrated that both hCG and FSH are required to achieve adequate spermatogenesis when the initial testicular volume is low (<4 ml). The mean and median pre-treatment testicular volumes in this trial were 4.3 and 4.5 ml. Although the efficacy of hCG alone in the patient population studied in Trial 6793 is uncertain, it is unlikely that hCG would have been as efficacious as the combination of hCG and Gonal-F.

The primary endpoint of the study (>1.5 x 10^6 spermatozoa/ml) represents a modest improvement in spermatogenesis. However, prior data have demonstrated that such a sperm count does not preclude fertility in men with HH. In this study, mean sperm counts in the completed treatment, completed protocol, and intent to treat groups were all greater

than 10 x 10^6 sperm/ml. Two "clinical" pregnancies (producing normal offspring) and 1 "biochemical" pregnancy occurred.

No drug related serious adverse events occurred. Several of the most common adverse events (including acne and gynecomastia) are recognized consequences of androgen therapy.

The reviewer believes that Trial 6793 does support the efficacy and safety of Gonal-F in combination with hCG for inducing spermatogenesis in men with HH.

5.0 Clinical Trial **GF 5844** ("A Phase 3, Multinational, Multicenter, Non-comparative Study to Assess the Safety and Efficacy of Recombinant Follicle Stimulating Hormone (Gonal-F) in Men with Isolated Hypogonadotrophic Hypogonadism") The study began in September, 1992, and ended November, 1997.

5.1 Objectives: 1) To assess the ability of Gonal-F in combination with Profasi to initiate spermatogenesis and achieve a density of mature sperm cells of at least 1.5 x 10^6 per ml in men with primary complete IHH and 2) To determine the safety and tolerability of Gonal-F administered SC in combination with Profasi in this patient population for 18 months.

5.2 Design and conduct summary: This protocol was a multinational, multicenter (2 United Kingdom, 3 France, 1 Germany), non-randomized, non-controlled, non-comparative, open label, escalating dose study to assess the safety and efficacy of recombinant human follicle stimulating hormone (r-hFSH, Gonal-F) administered subcutaneously in combination with human chorionic gonadotropin (hCG, Profasi) given intramuscularly or subcutaneously to induce spermatogenesis in men with HH. Thirty-two men aged 18 to 55 with HH and azoospermia were enrolled. Patients were allowed no T replacement for at least 5 weeks and/or no hCG replacement for a least 2 weeks prior to the pre-study assessment. Once the patient with HH (azoospermia and low T with low or normal LH and FSH) was entered into the study, he received hCG (Profasi) at a dosage of 2000 U twice a week for 3 months (pretreatment phase). The dose of hCG could be adjusted from month 2 onwards in order to maintain serum T levels within the normal range (minimum 9.0 nmol/l. The patient had to be azoospermic prior to entry into the treatment phase (hCG plus hFSH). If the patient did not produce a semen sample after the first 3 months of hCG, a further 3 months of hCG treatment was allowed during which time a semen sample had to be obtained. In addition to a semen analysis, at the end of the pre-treatment phase, the patient underwent a physical examination (including measurement of testicular size with a Prader orchidometer) and determination of serum T, FSH, inhibin, and E_2. During the treatment phase Gonal-F was administered subcutaneously at a dose of 150 IU 3 times weekly in combination with hCG 2000 U (or the dosage necessary to normalize serum T) twice weekly for 18 months. (According to the original protocol, Profasi was to be administered intramuscularly. However, during the course of the trial, Profasi was licensed for SC administration and the protocol was amended to allow administration by this route.) Following a protocol amendment in May, 1996, Gonal-F dosage was to be increased to 225 IU three times a week if the patient did

not respond in terms of the sperm count done at the 9 month visit. During Gonal-F treatment, patients were monitored for 18 months at 3 monthly intervals to assess safety and efficacy of therapy. Physical examination, serum T, FSH, inhibin, E_2, semen analysis, and evaluation of local injection tolerance were performed every 3 months. Hematology, chemistry, urinalysis, and anti-FSH antibodies were determined at months 3, 12, and 18.

Reviewer's comments: The starting dose of hCG 2000 U 2 times/week was the same as in trial 6410. The starting dose of hCG in trial 6793 was 1000 U every 2 days. The starting dose of Gonal-F was 150 IU 3 times/week compared to 150 IU 2 times/week in trial 6410 and 150 IU every other day in trial 6793. These minor dose variations are not considered clinically significant.
Unlike trials 6410 and 6793, trial 5844 was a "naïve" population in which patients who had received prior GnRH or FSH therapy were excluded.

5.3 Study population: Thirty-two men with primary IHH were enrolled. Patients were required to have had a washout period for other medication used to treat HH prior to enrollment and treatment. Twelve of the 32 patients (37%) had IHH with anosmia (*Kallmann's syndrome*). Seven of the 32 patients desired fertility, had partners and desired a pregnancy. The median age was 25.9 years.

5.4 Inclusion and exclusion criteria: Inclusion criteria included men aged 17 to 55. If the patient were less than 21 years of age, his bone age must have been documented to be greater than 15 years and/or he must have been confirmed to have anosmia. No T replacement therapy for at least 5 weeks and/or no hCG replacement therapy for at least 2 weeks prior to prestudy assessment was allowed. All patients were required to have the following serum hormone values: 1) cortisol > 155 nmol/l, LH <9.6 mIU/ml, FSH <14 mIU/ml, prolactin >40 and <290 mIU/l, T <5.2 nmol/l, free T4 >11 and <24 pmol/l, and TSH >0.43 and <3.8 uIU/ml. No previous therapy with FSH or GnRH was allowed. At study entry the patient was required to have azoospermia and have a mean testicular volume of <4 ml. Patients could have no pituitary or hypothalamic mass lesion as assessed by CT or MRI. No CT or MRI was required if the patient were anosmic. Exclusion criteria included 1) any disease that might modify the condition under study, such as diabetes mellitus, cardiomyopathy, hepatic or renal disease, or endocrine diseases such as Cushing's syndrome or hyperthyroidism 2) medical records documenting a serum T concentration of greater than 150 ng/dl and/or serum FSH and LH concentrations above the normal range at the time of the initial diagnosis of IHH 3) if previously treated with hCG to have required a total dose of more than 10,000 U per week to normalize serum T4) any past or current condition which could have led to testicular dysfunction (torsion or cryptorchidism) 5) any past or current condition which could have led to obstruction of the vas deferens 6) major varicocele (Grade 3 or 4) and 7) abnormal karyotype such as Klinefelter syndrome.

Reviewer's comments: Unlike trials 6410 and 6793, no prior GnRH or FSH therapy was allowed. Patients with a mean testicular volume of >4 ml were excluded. In trial 6793,

patients with a testicular volume of >6 ml were excluded and trial 6410 did not consider testicular size to be an exclusion criterion.

5.5 Primary and secondary endpoints: The primary endpoint was the proportion of patients who achieved a spermatozoa concentration of at least 1.5 x 10^6/ml. Secondary endpoints included changes in the following measurements: 1) mean testicular volume 2) serum inhibin concentrations 3) ejaculate volume 4) spermatozoa count per ejaculate 5) percentage of sperm with normal morphology 6) percentage of sperm with progressive motility and 7) pregnancy in partner (for couples desiring fertility).

Reviewer's comments: This trial, as well as Trials 6410 and 6793, used the proportion of patients who achieved a spermatozoa concentration of >1.5 x 10^6/ml as the primary endpoint. In patients with HH, fertility has been reported to occur with relatively low sperm densities.

5.6 Withdrawals, compliance, and protocol violations: Thirty-two patients entered the study. Ten of the 32 patients withdrew from the study over the two year period. Four patients (#'s 121, 401, 603, and 605) were withdrawn before the start of Gonal-F treatment because the entry criteria for the treatment phase were not satisfied. Two other patients (#'s 102 and 601) were found to be ineligible after they had started Gonal-F treatment. Two patients (#'s 103 and 108) withdrew during Gonal-F treatment because of non-compliance. (Patient # 103 was noncompliant with injections and was withdrawn after 12 months, having been hospitalized for a pulmonary lobectomy.) Another patient (# 122) was withdrawn by the investigator because of non-compliance after starting Gonal-F treatment, but before his first assessment. Another patient (# 301) was withdrawn after he was discovered to have received highly-purified urinary FSH (Metrodin) rather than Gonal-F. Three further patients who completed the study were deemed to be ineligible for the "evaluable" data set. Patients #113 and 114 had body mass index greater than the protocol limit and were entered as Product Donation patients (they were withdrawn from the study but continued to receive drug). As a result, some of their hormone values were not monitored as closely as the other patients. Patient # 124 had a solitary kidney and elevated serum creatinine.

Three patient populations were analyzed in the efficacy analyses: .

1) "All patients" included all 32 patients entered into the study.
2) "All-6 patients" included all patients minus 6 patients who did not receive Gonal-F or received the drug for a short period of time but left the study prior to any assessment.
3) "Evaluable patients" included the 19 patients who did not have major deviations from the eligibility criteria and/or the treatment procedures stated in the protocol.

All 32 patients who entered the study were included in the safety analysis.

Protocol violations: Seven of the 32 patients had major eligibility violations. Patient #'s 113, 114 , and 124 are discussed above. Patient # 102 was found to be cryptorchid and patients # 601, 603, and 605 had a prior history of orchidopexy. Seven of the patients had major protocol deviations during the trial. Patient # 121 was found to not be azoospermic

and Patient # 401 did not produce an end of pretreatment semen sample. Patient # 113 started Gonal-F although his serum T had not normalized. Patients # 103, 108, 122, and 301 are discussed above under withdrawals.

Reviewer's comment: Thirteen of the 32 patients had major eligibility violations or major protocol violations and were not included in the "evaluable" patient population. None of these "withdrawals" from the evaluable patient population were due to adverse events.

5.7 Efficacy analysis: The primary endpoint was the proportion of patients who achieved a spermatozoa concentration of >1.5 x 10^6/ml. The results for the evaluable patients are shown in Table 13. (The "evaluable" patients were those 19 patients who did not have major deviations from the eligibility criteria or treatment procedures.)

Table 13. Evaluable patients: proportion of patients who achieved a sperm density >1.5 x 10^6/ml.

Number of patients	Achieved	Not Achieved
19	12	7
%	63.2%	36.8%

Those secondary endpoints which, in the reviewer's opinion, are the most clinically relevant are presented below:

Table 14. Spermatozoa count per ejaculate (10^6) ("All-6" patient population)

Visit	N	Mean
Pre-treatment	23	0.00
3 months	22	0.43
6 months	23	0.49
9 months	23	3.80
12 months	25	6.34
15 months	23	13.11
18 months	22	32.53

Table 15. Percent of normal sperm forms in the ejaculate ("All-6" patient population)

Visit	Number of patients assessed	Mean % normal forms
3 months	2	35.00
6 months	5	20.00
9 months	10	39.10
12 months	11	46.55
15 months	12	39.08
18 months	13	45.92

Table 16. Percent of sperm with progressive motility ("All-6" patient population)

Visit	Number of patients assessed	Mean % of sperm with progressive motility
3 months	3	38.33
6 months	7	25.29
9 months	12	25.58
12 months	13	42.39
15 months	12	35.58
18 months	16	36.38

Table 17. Mean testicular volume (ml) ("All-6" patient population)

Visit	N	Mean
Pre-study	32	2.0
Pre-treatment	23	2.5
3 months	26	5.3
6 months	26	5.8
9 months	25	8.3
12 months	25	9.5
15 months	22	10.4
18 months	22	12.2

Table 18. Serum inhibin concentration (U/mL) ("All-6" patient population)

Visit	N	Mean
Pre-study	28	0.96
Pre-treatment	23	1.20
3 months	26	1.70
6 months	26	1.50
9 months	25	1.90
12 months	22	2.10
15 months	19	2.30
18 months	14	3.20

Table 19. Serum FSH concentration (mIU/mL) (normal range = 1-14 mIU/mL) ("All-6" patient population)

Visit	N	Mean
Prestudy	25	1.2
Pretreatment	23	1.0
3 months	26	2.9
6 months	26	2.4
9 months	26	3.3
12 months	25	2.6
15 months	23	2.9
18 months	22	3.7

Other secondary endpoints:

Pregnancy: Among the 7 couples who wished to conceive, 6 pregnancies occurred in the partners of 4 patients: 1) Patient # 101's partner became pregnant about 6 months after start of the patient's Gonal-F treatment. The patient's sperm density was 2.0 x 10^6/ml at the 3 and 9 month visits. She delivered a healthy baby boy. She conceived again after the patient had received 18 months treatment and 3 further months of treatment with Gonal-F on a named patient basis. The patient's sperm density was 100.0 x 10^6/ml at the 18 month visit. An ultrasound confirmed the pregnancy but the details of the delivery are not reported. 2) Patient # 105's partner became pregnant 6 months after the start of the patient's treatment. The patient's sperm densities were 0.0 and 1.0 x 10^6/ml at the 3 and 9 month visits. She delivered a healthy girl. 3) Patient #125's partner became pregnant 12 months after the patient began Gonal-F therapy. The patient's sperm density was 18 x 10^6/ml at the 9 month visit. She miscarried but conceived again after the patient had received 15 months treatment. The patient's sperm density was 2 x 10^6/ml at the 15 month visit. She delivered a healthy girl. 4) Patient #602's partner became pregnant after he had received 15 months treatment. The patient's sperm density was 36.1 x 10^6/ml at the 15 month visit. She delivered a healthy boy.

5.8 Safety analysis:

5.8.1 Extent of exposure: The extent of exposure to Profasi and Gonal-F during the treatment phase is depicted in table 20.

Table 20. Extent of exposure to hCG and r-hFSH during the treatment phase. (n=26)

Variable	Mean
Total hCG dose (x2000 U's)	270.0
Total hCG dose (U's)	540000
Total FSH dose (x150 IUs)	225.3
Total FSH dose (IUs)	33795

5.8.2. Serious adverse events: There were no study deaths. Four serious adverse events were reported in 4 patients.

1) Patient #102 underwent left inguinal exploration for a non-palpable testis. His testis (?both testes) had been previously palpable. Prior to surgical exploration, an MRI had located his testes (? or just left testicle) in the inguinal canal. At exploration, "what had appeared to be retractile testes (testis?) were in fact prolapsing, fat-laden vasa deferentia and the testes were thought to have always been cryptorchid." (Prior to the surgical exploration, "it was felt that the increased testicular size induced by hormonal treatment had led to the testes becoming lodged in the retracted position.") The investigator considered the event possibly related to study medication.
   Reviewer's comment: The reviewer does not understand the specifics of this case but believes that any relationship to study drug is remote.
2) Patient #103 had a two year history of bronchiectasis with pulmonary hemangioma following a sporting injury. After 5 months treatment with Gonal-F, he had an episode of hemoptysis and underwent a right middle and lower pulmonary lobectomy.
   Reviewer's comment: The reviewer agrees with the investigator that this event was not related to study drug.

3) Patient #107 underwent surgical excision of an infected pilonidal sinus. *Reviewer's comment: The reviewer agrees with the investigator that this event was not related to study drug.*
4) Patient #201 underwent excision of a cervical lymph node with benign pathology. The patient had perceived the enlarged lymph node prior to study entry but believed that the node had enlarged. Serology was positive for Epstein-Barr virus. *Reviewer's comment: The reviewer agrees with the investigator that this event was not related to study drug.*

5.8.3 Discontinuation due to adverse event: There were no discontinuations due to adverse events during the study.

5.8.4 Frequent adverse events: A total of 22 non-serious adverse events were reported in 14 patients. Fourteen of these events were considered by the investigators to be possibly or probably related to study drug. Three non-serious events were thought to be probably related to study drug. These three consisted of 2 cases of acne and one case of gynecomastia. Both cases of acne occurred during the first 3 months of treatment with Gonal-F. There were 5 reports of varicocele in 4 patients. Patient #104 experienced a bilateral grade 1 varicocele, graded mild at treatment month 15. Patient #111 had an ungraded varicocele at Month 18. Patient #115 experienced a grade 1 varicocele (mild). Patient #112 experienced separate right and left varicoceles at months 9 and 15. Other adverse events thought to possibly be related to study drug were mild headache, "feeling cold," and elevated alkaline phosphatase.

Reviewer's comment: It is uncertain as to whether the varicoceles were a drug related adverse event or were pre-existent and discovered by repeated physical examinations.

The assessment of local reactions per injection showed that 98.4% of 5762 injections caused no or a mild reaction. Seven reactions in 4 patients were reported as "severe." These "severe" reactions consisted of swelling, redness, bruising, and/or pain. These reactions did not lead to treatment modification or withdrawal.

5.8.5. Changes in laboratory values: The only consistent change in hematologic parameters was an increase in parameters of erythropoiesis. Hemoglobin increased from 14.1 g/dl at pretreatment to 14.7 g/dl after 3 months, 15.0 g/dl after 12 months, and to 14.9 g/dl after 18 months. Hematocrit also increased from 44.7% at pre-treatment to 46.8% at 3months, 47.6% at 12 months, and to 47.1% after 18 months. The sponsor believes that this increase in erythropoiesis, wherein all measurements remained within normal range, is an expected result of increased serum testosterone levels during therapy. The only consistent change in chemistry values was an increase in serum creatinine from a pre-treatment mean of 80.6 umol/l to 86.4 umol/l after 3 months, 89.5 umol/l after 12 months, and to 91.8 umol/l after 18 months. All of these values are well within normal limits (25.52-132.6 umol/l). Only 1 patient had a laboratory abnormality that was considered "possibly related to trial medication." Patient 401 had an elevated alkaline phosphatase level (437 IU/l; normal range 80-220 IU/l) at the end of pretreatment. The

patient withdrew from the study at that visit for an unrelated reason (he was not able to produce a semen sample).

Reviewer's comment: The reviewer agrees that the minimal elevations in hemoglobin and hematocrit are expected effects of increased testosterone levels. Direct association of Gonal-F and the single case of increased alkaline phosphatase is not possible.

All test results for antibodies to r-FSH were negative.

5.9 Reviewer's assessment of safety and efficacy in Trial 5844:
Like Trials 6793 and 6410, Trial 5844 was not controlled and there was no comparator arm. Because of the rarity of spontaneous resolution of this disorder, the stable nature of the deficiency, and the objective efficacy measures obtained, the reviewer agrees with the sponsor that the non-comparative design of the study is acceptable. The use of a placebo control was considered unethical for the prolonged duration of exposure during the study. The use of a comparator arm would have significantly reduced the number of evaluable patients with this rare disorder in the study drug arm.

HCG alone has been reported to induce spermatogenesis in men with HH. In general, however, men with an initial testicular volume <4 ml require both hCG and FSH to induce adequate spermatogenesis. In Trial 5844, patients with a testicular volume of greater than 4 ml were excluded. Although the primary endpoint of $>1.5 \times 10^6$/ml spermatozoa is modest, the mean spermatozoa count per ejaculate at 18 months treatment with Gonal-F was 32.53×10^6.
There were no serious adverse events related to study drug and no study discontinuations related to adverse events. Two cases of acne and one case of gynecomastia were thought to be related to study drug. In addition, 4 patients developed varicocele (or had a pre-existing varicocele which was detected during therapy). The mild increases in hematocrit and creatinine are consistent with known effects of androgen therapy.

The reviewer believes that Trial 5844 does support the efficacy and safety of Gonal-F in combination with hCG for inducing spermatogenesis in men with HH.

6.0 Clinical trial **GF 6410** ("A Phase 3, Multicenter, Non-comparative Study to Assess the Safety and Efficacy of Recombinant Human Follicle Stimulating Hormone (Gonal-F) in Combination with Human Chorionic Gonadotropin in Inducing Spermatogenesis in Men with Severe Hypogonadotrophic Hypogonadism")

6.1 Objectives: 1) To assess the ability of Gonal-F in combination with Profasi to initiate spermatogenesis and achieve a density of mature sperm of at least 1.5×10^6/ml in men with HH and 2) to determine the safety and tolerability of Gonal-F in combination with Profasi in this patient population for 18 months.

6.2 Design and conduct summary: This protocol was a multicenter (2 Australian sites) non-randomized, non-controlled, non-comparative, open label, escalating dose study to assess the safety and efficacy of recombinant human FSH (r-hFSH, Gonal-F)

administered subcutaneously in combination with hCG (Profasi) administered subcutaneously to induce spermatogenesis in men with HH. Ten men (aged 18 to 55) with HH and azoospermia were enrolled. No T replacement for at least 5 weeks and/or no hCG replacement was allowed for at least 2 weeks prior to the prestudy assessment. During the pretreatment phase, patients received hCG (Profasi) at a dose of 2000 U twice a week for 3 months. The dose of hCG could be adjusted from month 2 onwards in order to maintain T concentrations within the normal range. Azoospermia (defined as a sperm density of $<0.1 \times 10^6$/ml) was confirmed prior to entry into the treatment phase (hCG and r-hFSH). If this weren't possible after the initial 3 months of hCG, a further 3 months of hCG treatment was allowed during which time a semen specimen had to be obtained. At the end of pre-treatment, physical examination (including measurement of testicular size using a Prader orchidometer) and assessments of serum T, FSH, inhibin B, E_2, hematology, chemistry, urinalysis, semen analysis, and baseline assays for anti-FSH antibodies were performed. Following the pre-treatment phase (up to 6 months), patients who had serum T levels within the normal range and were still azoospermic were eligible to enter the treatment phase. During the treatment phase, patients were administered Gonal-F subcutaneously at a dose of 150 IU 3 times weekly in combination with hCG 2000 U (or the dose necessary to normalize serum T) subcutaneously twice weekly for 18 months. If a patient responded poorly to r-FSH, the dose could be increased to a maximum of 150 IU daily. During Gonal-F therapy, patients were monitored for 18 months at 3 monthly intervals to assess safety and efficacy of the drug. Serum T, FSH, inhibin B, and E_2 were measured at months 3, 6, 9, 12, 15, and 18. Hematology, chemistry, urinalysis, and anti-FSH antibodies studies were performed at months 3, 12, and 18. A semen analysis was performed at months 3, 6, 9, 12, 15, and 18.

Reviewer's comments: The starting dose of hCG was 2000 U twice per week compared to the same dose in Trial 5844 and to 1000 U every 2 days in Trial 6793. The starting dose of Gonal-F was 150 IU twice a week compared to 150 IU 3 times per week in Trial 5844 and 150 IU every 2 days in Trial 6793. The variations are not considered clinically significant.

6.3 Study population: Ten patients with HH were entered into the study. All patients wished to become fertile. The mean and median patient ages were 36 and 37 years. The oldest patient was 48. Five of the 10 patients had received prior GnRH or FSH. Two of the 10 patients were anosmic.

6.4 Inclusion and exclusion criteria: Inclusion criteria included men aged 17 to 55. If the patient had not reached age 21, his bone age must have been confirmed to be greater than 15 years and/or he must have been confirmed to be anosmic. No T replacement for at least 5 weeks and/or no hCG therapy for at least 2 weeks prior to prestudy assessment was allowed. A below normal serum T level (<10 nmol/l) and azoospermia ($<0.1 \times 10^6$/ml) as shown by semen analysis performed within 2 months prior to entry into the pretreatment phase were required.

Exclusion criteria included 1) any disease that could modify the condition under study such as diabetes mellitus, cardiomyopathy, hepatic or renal disease, or endocrine diseases

such as Cushing's syndrome or hyperthyroidism 2) medical records documenting a serum T concentration greater than 10.0 nmol/L and/or serum FSH and LH concentrations above the normal range at the time of initial HH diagnosis 3) if previously treated with hCG, a requirement for a total dose of more than 10,000 U per week to normalize serum T levels 4) any medical condition which could have led to testicular dysfunction 5) any condition which could have led to vas deferens obstruction (eg. epididymitis) 6) major varicocele (grade 3 or 4) and 7) abnormal karyotype such as Kleinfelter's syndrome.

Reviewer's comment: No testicular size criterion is included. At baseline, mean testicular volumes ranged from 1.5 to 11 ml (mean=4.5). Seven patients had a mean testicular volume <4 cc. Three of the patients, therefore, had testicular volumes which are not consistent with the patient populations in Trials 6793 and 5844. The reviewer does not believe that these three patients are confounding. In addition, some patients may have had a few sperm on semen analysis (azoospermia was defined as <0.1 x 10^6 sperm/ml).

6.5 Primary and secondary endpoints: The primary endpoint was the proportion of patients who achieved a spermatozoa concentration of >1.5 x 10^6/ml. Secondary endpoints were changes in the following measurements: 1) mean testicular volume 2) serum inhibin B concentrations 3) ejaculate volume 4) sperm count per ejaculate 5) percentage of sperm with normal morphology 6) percentage of sperm with progressive motility and 7) incidence of pregnancy.

Reviewer's comment: The primary endpoint is the induction of a modest sperm count. In patients with HH, fertility has been reported to occur with relatively low sperm densities.

6.6 Withdrawals, compliance, and protocol violations: Ten patients started the study and three withdrew. Two patients stopped at the end of the pre-treatment period: patient 107 withdrew because his serum T level was not normalized within 6 months of beginning hCG therapy and Patient 206 withdrew when he was found to be ineligible. The third patient withdrew at the end of 12 months of Gonal-F therapy because he had no response to treatment, remaining azoospermic, and wished to stop therapy.
Two patient populations are analyzed in the efficacy analysis:
1) "All patients" which included all 10 patients
2) "Evaluable patients" which included 8 patients (the 2 patients who did not receive Gonal-F were omitted)

For the safety analysis, the "all patient" population was used.

Protocol violations: None of the 8 evaluable patients had a major protocol violation. Two of the evaluable patients had minor protocol deviations. Patient #110 had a T level of 9.3 nmol/l but continued into the treatment phase. Another patient (#209) had a final T value of 3.8 nmol/l which was thought to be a laboratory error. A later measurement was 14.3 nmol/l.

6.7 Efficacy analysis: The primary endpoint was the proportion of patients who achieved a spermatozoa concentration of >1.5 x 10^6/ml. These results are shown in Table 21.

6.7 Efficacy analysis: The primary endpoint was the proportion of patients who achieved a spermatozoa concentration of >1.5 x 10^6/ml. These results are shown in Table 21.

Table 21. Evaluable patients: Proportion of patients achieving a sperm density of >1.5 x 10^6/ml.

Number of patients	Achieved	Not Achieved
8	5	3
	62.5%	37.5%

Secondary endpoints:

Table 22. Total sperm count (x10^6) per ejaculate

Visit	N	Mean
3 month	7	0.2
12 month	8	23.8
18 month	7	25.8

Table 23. Percent of normal sperm forms in the ejaculate

Visit	Number of patients assessed	Mean % normal forms
3 month	1	28.0
12 month	5	7.6
18 month	7	7.4

Table 24. Percent of sperm with progressive motility (WHO grade A+B)

Visit	Number of patients assessed	Mean % of sperm with progressive motility
3 month	2	33.0
12 month	6	27.2
18 month	7	24.3

Table 25. Mean testicular volume (ml)

Visit	N	Mean
Pre-study	8	4.8
Pre-treatment	8	5.6
3 month	8	7.4
12 month	8	9.3
18 month	7	9.6

Table 26. Serum inhibin B concentration (pg/ml)

Visit	N	Mean
Pre-treatment	8	49.4
3 month	8	60.3
12 month	8	65.2
18 month	7	78.0

1) Patient #101's partner became pregnant 18 months after the start of the patient's Gonal-F treatment. The patient's sperm density was 0.6 x 10^6/ml at month 15 and 3.5 x 10^6/ml at the 18 month visit. A healthy baby boy was delivered.
2) Patient #102's partner became pregnant 12 months after the start of the patient's Gonal-F treatment. The patient's sperm density was 2.7 x 10^6/ml at the 9 month visit and 10 x 10^6/ml at the 12 month visit. A healthy baby boy was delivered.
3) Patient #209's partner underwent IVF/ICSI during the course of the study. She became pregnant (confirmed by ultrasound) but miscarried. The patient was azoospermic until the Month 12 visit when sperm density was reported as <0.01 x 10^6/ml. The patient was azoospermic at Month 15.

6.8 Safety analysis:

6.8.1 Extent of exposure: The extent of exposure to Profasi and Gonal-F exposure is depicted in Table 27.

Table 27. Extent of Profasi and Gonal-F exposure during the pretreatment and treatment phases.

Phase	Variable	Mean	Max.
Pre-treatment (N=10)	Total hCG dose (U)	88600	160000
Treatment (N=8)	Total hCG dose (U)	556200	924000
Treatment (N=8)	Total FSH dose (IU)	36270	46500

6.8.2. Serious adverse events: There were no study deaths. One serious adverse event was reported (patient #103). This 50 year old man had HH diagnosed at age 17. He started hCG as part of the study treatment on February 1, 1994 at a dose of 4000 U/week. This dose was increased to 6000 U/week on May 2 1994 when he also started FSH treatment at 450 IU/week. On February 1, 1995, after 9 months therapy with Gonal-F, he underwent surgery for removal of breast tissue, which was first noted to be present on December 22, 1993. He was noted to have similar symptoms of development of breast tissue during previous therapy with GnRH. The pathology report revealed gynecomastia and no atypia. The investigator considered the incident of no clinical significance and unrelated to the study medication.

Reviewer's comment: The reviewer believes that this adverse event is possibly related to study drug.

6.8.3. Discontinuation due to adverse events: There were no discontinuations due to adverse events.

6.8.4. Frequent and other adverse events: Two other adverse events were reported, both in the same patient (#102). One adverse event was a mild upper respiratory infection and the other was mild retrosternal pain. Both events were considered by the investigator to be unrelated to the study medication.

Local injection reactions to Gonal-F: A total of 1930 Gonal-F injections were administered during the study. 98.1% lead to either no or mild reaction. Four injections resulted in "severe" reactions, reported by 2 patients, all involving injection site pain. The assessment of local reactions per patient showed that 6 of 8 patients reported no local reaction or mild reaction to injections. Two patients reported at least 1 severe reaction (pain) which did not result in treatment modification.

6.8.5. Changes in laboratory values: Assessment of hematology, chemistry and urine before, during, and after therapy did not show any clinically relevant changes.

Anti-FSH antibody assay results before, during, and after the study were all negative.

6.9 Reviewer's assessment of efficacy and safety:

This trial, like Trial numbers 6793 and 5844, was not controlled and had no comparator arm. For the reasons discussed under 4.9 and 5.9, the reviewer believes that this is acceptable. Although the primary endpoint of the study was a modest improvement in spermatogenesis (>1.5 x 10^6 spermatozoa/ml), the mean sperm count per ejaculate was 25.8 x 10^6. No serious adverse events related to study drug and no discontinuations due to adverse events occurred.

The reviewer believes that Trial 6410 does support the efficacy and safety of Gonal-F in combination with hCG for inducing spermatogenesis in men with HH.

7.0 Overview of Efficacy: Fifty-six of the 72 patients enrolled in the three studies actually received Gonal-F. None of the three trials were placebo controlled and none included a comparator arm. In view of the rarity of HH, the stable nature of the deficiency, and the objective efficacy measures employed in these studies, the sponsor suggests that a non-comparative study design is acceptable. In addition, the use of a placebo control was considered unethical for the prolonged duration of exposure that such a study design would entail. The use of a comparator treatment group would have significantly reduced the number of evaluable patients with this rare disorder in the study drug arm. The reviewer agrees that the study design is acceptable.

The effect of hCG treatment alone on spermatogenesis was not addressed in any of the three trials. Prior data have indicated that hCG alone can induce spermatogenesis in some men with HH. In these prior reports, the most important factor in determining spermatogenic response to hCG alone was pretreatment testicular size. In one previously published study, all patients who responded to hCG alone had an initial testicular volume of > 4 ml. In another study, all men who had a testicular volume <4 ml and produced sperm with hCG therapy alone had sperm counts of <1 x 10^6/ml. In Trials 6793, 5844, and 6410, mean testicular volume was 4.4, 2.0, and 4.5 ml respectively. The lower mean testis volume in Trial 5844 probably reflects the fact that patients with prior gonadotropin therapy were excluded. The low pre-treatment testicular volumes in the three studies makes response to hCG alone unlikely.

The dose of 150 IU of Gonal-F three times per week was chosen because of data derived from pharmacokinetic studies of Gonal-F in males and from prior data derived from studies of urofollitropin (Fertinex, purified FSH derived from post-menopausal urine). In Trial 6793, 7 patients increased the hCG dose during the pretreatment phase of the study. Five of the 7 patients increased the dose from 1000 U every 2 days to 1500 U every 2 days. The other 2 patients increased the dose from 1000 U to 1500 U and finally to 2250 U. In Trial 6973, eight patients increased the Gonal-F dose during the treatment phase. Six patients increased the dose from 150 IU to 225 IU every 2 days. Two patients increased the dose from 150 IU to 225 IU and finally to 300 IU. In Trial 5844, 3 patients increased the dose of Gonal-F from 150 IU to 225 IU (2 patients after 12 months and 1 patient after 17 months).

The percentage of patients who received Gonal-F who achieved $>1.5 \times 10^6$ spermatozoa/ml in Trials 6793, 5844, and 6410 was 63.6%, 46.2%, and 62.5% respectively. Although this primary endpoint represents only a modest increase in sperm concentration, a sperm concentration of $>1.5 \times 10^6$/ml has been reported to achieve pregnancy in 92% of men with HH treated with hCG and menotropins.

Secondary endpoints of mean testicular volume, total sperm count, and mean sperm concentration were supportive of drug efficacy (Table 28):

Table 28. Secondary endpoints in the three trials

	Trial 6793 (N=22)	Trial 5844 (N=26)	Trial 6410 (N=8)
Mean testicular volume (ml)			
End pre-treatment	7.1	2.5	5.6
Month 18	16.8	12.2	9.6
Mean total sperm count (x 10^6)			
End pre-treatment	0.0	0.0	0.0
Month 18	46.8	32.5	25.8
Mean sperm concentration (x 10^6)			
End pre-treatment	0.0	0.0	0.0
Month 18	14.8	16.2	8.5

Twelve pregnancies were achieved in 10 patients' partners of the 37 patients who were seeking pregnancy. Eight pregnancies continued to term and 8 healthy babies were born.

8.0 Overview of Safety: There were no study deaths, no serious adverse events related to study drug, and no study discontinuations due to adverse events related to study drug. The most common adverse event was acne (reported in 50% of patients in Trial 6793, 9% in Trial 5844, and 0% in Trial 6410). Breast pain and gynecomastia were reported in 13.6% and 9.1% of patients in Trial 6793. Testicular pain was reported by 13.3% of

patients during the pre-treatment phase of Trial 6793 and five varicoceles were reported in 4 patients in Trial 5844. Hematologic and chemistry changes (hematocrit and creatinine elevations over baseline but still within normal limits) are known effects of androgen therapy.

9.0 Recommendations for Regulatory Action: The reviewer recommends that Gonal-F be approved for induction of spermatogenesis in men with primary and secondary HH and in whom the cause of infertility is not due to primary testicular failure.

10.0 Recommendations for Revised Labeling:

1) The dose of hCG and possible dose escalation to achieve normal T levels should be more clearly addressed. It is not clear whether or not IU and U USP are equivalent units for hCG.
2) Dose escalation of Gonal-F in patients with persistent azoospermia should be more clearly addressed.

The process of label revision is ongoing at the time of this review.

/S/

George S. Benson, MD
Medical Officer

4/28/00

I concur with this review and I also recommend approval of this new indication for Gonal-F (see my memo dated 4/28/00)

/S/
Acting Team Leader, Urology
4/28/00

NDA 20-378 S-006

Clinical Review of Updated NDA Safety Material

Submitted: May 17, 200
Received: May 17, 2000
Review completed: May 17, 2000

Drug Product: Gonal-F
Sponsor: Serono Laboratories
Indication: Induction of spermatogenesis in men with hyopogonadotropic hypogonadism and in whom the cause of infertility is not primary testicular failure.

Background: The original submission for this supplemental NDA, (Gonal F for induction of spermatogenesis in men with hyopogonadotropic hypogonadism and in whom the cause of infertility is not primary testicular failure), contained complete and final information for two of three controlled clinical trials. The third study, Clinical Study 6793, was still in progress at the time of submission. Of 30 enrolled American patients, nine patients were still participating in the trial at the time of original submission.

At this time, the sponsor submits updated safety information on these 9 patients, from the time of data cut-off for the original NDA database (March 11, 1998) up to today's date (May 17, 2000). Of these 9 patients, seven have completed the trial and only 2 remain on study.

Materials reviewed: The sponsor submitted a nine-page document containing updated information regarding all spontaneously reported adverse events for these nine patients and updated efficacy information for these nine patients.

Review of safety information:
There were a total of 88 adverse event reports in nine patients.

Deaths: There were no deaths reported.

Serious adverse events: There were no serious adverse events reported.

Adverse events leading to discontinuation: There were no adverse events reported which led to discontinuation.

Severe adverse events: There were two adverse events coded as "severe" in intensity. Patient #2030008 reported severe abdominal cramps on 1/01/98. This event resolved on 2/14/98 and was considered "unrelated" to study medication. The event did not require intervention. Patient 2020004 reported severe gastritis on 11/20/98. The event is ongoing. The event has not required intervention. The event was judged as having a "possible" relationship to study drug.

> **Reviewer's comment: There does not appear to be a plausible relationship between Gonal-F therapy and abdominal cramps or gastritis.**

There were a total of 88 adverse event reports by these nine patients. Of these, 33 events were considered "not-related" to study medication. Table 1 describes the remaining 55 adverse events, which were of "unknown", "possible" or "probable" relationship to study drug:

Table 1. Adverse event reports of "unknown", "possible" or "probable" relationship to study drug in the safety update

Reported event	Number of reports
Acne	22
Testicular discomfort	6
Breast tenderness	5
Fatigue	4
Sleepiness	2
Gastritis	2
Muscle spasms	2
Gynecomastia	1
Injection site pain	1
Increased alkaline phosphatase	1
Increased size of pituitary adenoma	1
Scaly papules on back/flanks	1
Heart murmur	1
Rash	1
Increased aggressiveness	1
Rectal discomfort	1
Indigestion	1
Insomnia	1
Variable libido	1
Total	**55**

Of the 55 possibly related adverse events, 45 were coded as "mild" in intensity, 9 were coded as "moderate" in intensity and 1 was coded as 'severe" (see "severe adverse events" section above).

Of the nine events coded as "moderate" in intensity, there was one report of moderate gastritis (same patient as "severe" gastritis above), one report of moderate "increased aggressiveness", one report of moderate "pain at the injection site", and six reports of moderate "acne".

Reviewer's comments:

1. **The adverse events reported in this safety update are similar in type, in frequency, and in severity to those previously reported in the initial NDA submission.**
2. **Patient 2030008, in whom an "increased size of pituitary adenoma" was reported, may not have had a pituitary adenoma at all, based on a questionable MRI scan.**

Review of efficacy information:

The sponsor provided information regarding all semen analysis collected from these 9 patients from the initiation of the trial to today's date (May 17, 2000).

All 9 patients had entered the Gonal-F treatment period with no sperm in the ejaculate (azoospermia).

Of these 9 patients. 6 (66.6%) achieved the primary endpoint; that is, attaining 1.5 million sperm per milliliter of semen. Two patients were still azoospermic. One patient had attained only 1.4 million sperm per milliliter of ejaculate on his last semen analysis (dated 12/30/98).

The secondary endpoints, including total sperm per ejaculate, percentage of sperm with normal forms, and percentage of sperm with adequate motility appeared to improve during the Gonal-F treatment period in all 7 patients who attained sperm in the ejaculate.

> **Reviewer's comment: These efficacy data are consistent with those from the original NDA submission. These data support the decision to approve Gonal-F for this indication.**

Clinical summary: The safety and efficacy data provided in this safety update are consistent with the information provided in the original supplemental NDA application. There are no new safety or efficacy concerns. The data provided in this update support the decision to approve Gonal-F for this indication.

/S/

Mark S. Hirsch, M.D.
Acting Urology Medical Team Leader

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Serono Laboratories, Inc.

Statistical Review

No statistical review is required per the attached memorandum from Kate Meaker, Statistician, dated August 11, 1999.

Screening of New NDA
Division of Biometrics II

Date: AUG 1 1 1999

NDA #: 20-378

Priority Classification: S

Trade Name: GONAL-F

Applicant: Serono Labs

Generic Name: follitropin alfa for injection

Date of Submission: 7/27/99

Indication: male hypogonadotropic hypogonadism (HH)

No. of Controlled Studies: 0

No. of Uncontrolled Studies: 3

User Fee Goal Date: 7/27/2000

Date of 45-Day Meeting: 9/1/99

Medical Officer: Norman Marks, M.D.

Project Manager: Freshnie DeGuia

Screened by: Kate Meaker, M.S.

Volume numbers in statistical section: 12.30 – 12.44

Anticipated Review Completion Date: No statistics review

Comments:

This NDA includes 3 efficacy studies: GF 5844, GF 6410, and GF ~~6410~~ 6793. All are single-arm, non-comparative studies. There are no comparisons, tests, or other statistical methods applied for these studies. Therefore there will be no statistics review of this NDA.

/S/

Statistical Reviewer

Concur: Dr. Kammerman 8/11/99

Clinical Pharmacology & Biopharmaceutics Review

NDA:	20-378 (S006)
Product Trade Name:	Gonal-F® (follitropin alfa for injection)
Active Ingredient/s:	Recombinant Human Follicle-Stimulating Hormone (r-FSH)
Indication:	Male hypogonadal hypogonadism
Submission Date:	July 27, 1999
Sponsor:	Serono Laboratories Inc.
Type of Submission:	Supplemental NDA
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

Synopsis

Serono has submitted this supplemental NDA to seek approval for the use of 150 IU r-FSH three times a week (up to a maximum of 300 IU/week) in men for the treatment of hypogonadal hypogonadism. Included are results from three distinct pharmacokinetic (PK) studies designed to either assess single and multiple dose PK of r-FSH, or bioequivalence between the 75 IU and 150 IU formulations (all performed in healthy volunteers).

Background

Gonal-F® (follitropin alfa for injection) is a human FSH preparation of recombinant DNA origin developed and marketed by Serono for the induction of follicular development and ovulation in women with oligo-anovulatory infertility and for multiple follicular development for women undergoing assisted reproductive technology procedures, such as *in vitro* fertilization/embryo transfer. In addition to the above indications in women, Serono has submitted this supplemental NDA for the induction of spermatogenesis in men with primary and secondary hypogonadal hypogonadism .

Recommendation

Based on the review, NDA 20-378 (S006) is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective

/S/ Dated 5/17/00

Dhruba J. Chatterjee, Ph.D.,
Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D. /S/ Dated 5/17/00

CC: NDA 20-378 (S006), HFD 870 (S. Huang, A. Parekh, DJ. Chatterjee), HFD-580 (G. Benson, F. DeGuia), CDR (B. Murphy for drugs).

Table of Contents

Background

FSH is one of the key hormones regulating reproductive functions both in female and male mammals including humans. FSH is synthesized by gonadotropic cells of the anterior pituitary gland and is secreted into the general circulation. In females, it stimulates the growth and maturation of ovarian follicles, and in males it promotes spermatogenesis. Human FSH has been used as a therapeutic agent since the early 1960s. Currently, its main indications are: (a) in the female, for the stimulation of follicular development to restore fertility of anovulatory patients and the stimulation of multiple follicular development in ovulatory patients undergoing assisted reproductive technology (ART) such as *in vitro* fertilisation embryo transfer (IVF-ET), (b) in male, to initiate or restore spermatogenesis in patients suffering from hypogonadotropic hypogonadism.

Several pharmaceutical preparations of human FSH have been developed. Initially, gonadotropins extracted from pituitary glands were used. Later, gonadotropins extracted from the urine of postmenopausal women (hMG) containing equivalent amounts of urinary human FSH (u-hFSH) and of urinary human LH (FSH 75IU: LH 75IU) became standard preparations. About 10 years ago a preparation of u-hFSH (Metrodin), practically devoid of LH activity (FSH 75 IU: LH <0.7 IU), was developed to replace hMG in ART and to treat World Health Organization group II (WHO II) anovulation.

Recently, *in vitro* production of large quantities of human FSH suitable for pharmaceutical use has been achieved. Because FSH needs to be glycosylated, recombinant human FSH (r-hFSH, Gonal-F®, Laboratories Serono, Aubonne, Switzerland), is produced by a genetically engineered Chinese hamster ovary (CHO) cell line (a cell line of mammalian origir

Gonal-F® is a human preparation of recombinant DNA origin currently marketed for the induction of follicular development in women undergoing ART procedures, such as IV-FET. The sponsor has submitted the current supplemental NDA to market the same for induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism.

Review of Human PK/Biopharmaceutics Studies

Three main PK studies have been submitted in this application as below:

(i) Single Dose Pharmacokinetic Study of Gonal-F® in Males (Study 5665)
(ii) Multiple Dose Pharmacokinetic Study of Gonal-F® in Males (Study 5826)
(iii) Bioequivalence (BE) of 75 and 150 IU Formulations of Gonal-F® (Study 6570)

Based on the background of this submission, the following important questions should be critical with regards to an OCPB review (in the order of relevance):

Q. Have separate clinical trials been submitted in this application?

A. Yes. Results from multiple clinical studies have been submitted in this application to support efficacy and safety of Gonal-F® for this new indication.

Q. Is the clinical formulation same as the 'to-be-marketed'?

A. Yes. This was also clarified in a facsimile from the sponsor (Appendix 1).

Q. What is the intended dose? Do we have PK information in the target population from the intended dosing regimen?

A. The regimen, as described in the label, will generally be 150 IU three times a week (upto a maximum of 300 IU per day, depending on the patient response).

Although PK of r-FSH in the patient population was not determined for this application, the clinical trials (for evaluation of safety and efficacy) were performed in the target population. All PK information in this supplemental application was obtained in young healthy volunteers (age ≈ 20 – 29 years). The intended use of the drug being in young, infertile, otherwise healthy men, the choice of the population used in the PK studies is acceptable.

PK information is available from a multiple dose study performed with 225 IU per day for 7 days, steady state being achieved in 4-5 days. This regimen was more rigorous than what will be the actual general usage (according to label). Moreover, we do have single dose information on the 300 IU dosage from the bioequivalence study (Study 6570). Based on this, and the fact that the exposures achieved were significantly lower than an already marketed urinary FSH product (u-FSH), the PK information included is acceptable.

Q. How do the PK parameters for r-FSH appear?

Following single dose administration of 225 IU Gonal-F® (150 IU immunoassay dose) and subsequent data fitting and PK analysis, C_{max} of r-FSH was 2.5 IU/L, AUC - 220 IU*hr/L, $T_{½}$ - 41 hrs, and MRT 77 hrs. These were the mean values for 3 patients (only those patients for whom data could be fitted to a one-compartment model). It is to be noted that the exposure from Gonal-F® (based on C_{max} and AUC) was considerably lower than the marketed product u-FSH (based on a PK comparison in the same study).

Following administration of multiple doses, $T_{½}$, MRT and AUC of Gonal-F® were comparable to that obtained from the single dose study. An accumulation factor of 3 was reported. Steady state was achieved within 4-5 days. Apparent volume of distribution and clearance were also similar for the single and multiple dose studies.

A bioequivalence study was performed to compare the Gonal-F® formulations of two doses (75 and 150 IU) in 12 healthy male volunteers. Results have been presented both before (observed values) and after correction (reduced values) of baseline FSH. The analysis of the results for bioequivalence was not exactly according to the agency guidance. It appears that the data was not log-transformed, and the ANOVA was performed on the actual AUC and C_{max} values. However, from the results of the analysis (both observed and reduced) and the mean plots of the plasma profiles, it appears that the two formulations are bioequivalent, and are statistically indistinguishable. Both the formulations were used in the pivotal clinical trials.

To get an estimate of dose proportionality, one may compare the single dose PK data (following a 225 IU dose) versus the BE study data (following a 300 IU dose). The corrected immunoassay dose was not reported for the latter. Nevertheless, the mean exposure values are proportional to the uncorrected doses of 225 IU (C_{max} - 2.5 IU/L and AUC - 220 IU*hr/L) to 300 IU (C_{max} ≈ 3.5 IU/L and AUC ≈320 IU*hr/L).

Please refer to Appendix 2 for details of study design and results for all the PK studies.

Q. What other PK-related information is relevant to labeling?

- *PK-PD*: Two other minor studies (Study 5901 and 6063) were conducted to gather limited exposure-response information. In these studies, the effect of Gonal-F®on Inhibin B and steroidogenesis in healthy males were evaluated. From study 6063 (submitted as published literature), sponsor concludes that inhibin B (a unique testicular product undetectable in orchidectomized men) is responsive to the r-FSH stimulation, and reciprocal relationship exists with FSH in men with various forms of testicular diseases. Study 5901 indicates that r-FSH may influence changes in testicular steroidogenesis, thus rationalizing use of FSH in spermatogenic disorders. The sponsor has submitted results from separate and complete clinical trials for efficacy and safety determinations, and the results from the PK-PD studies not were utilized for any critical decisions related to efficacy or safety, or labeling claims. No PK-PD modeling was performed. Additionally, studies aimed at evaluating time and FSH dose dependent increases in sperm count would have been of interest.

- *Gender/Race issues*: Comparing PK parameters to those reported in the approved label for Gonal-F® for healthy female volunteers, the PK parameters are similar to that obtained in men in the current studies. AUC, C_{max}, T_{max}, $T_{½}$, calculated apparent Cl and V_{ss}/F and %F values are comparable (within statistical limits) to those obtained in men. These current studies in men were conducted in Japan. At our request, the sponsor has analyzed PK data obtained in various studies in different races, and statistically compared for PK differences in

them (Appendix 3). Based on this data, it can be inferred that there are no major differences in PK parameters between Caucasians and Asians.

- *Special Populations*: PK studies in populations with renal or hepatic disorders have not been conducted. The drug will be used in young, infertile, otherwise healthy men. So, a study in such special populations is not warranted. Moreover, the disease condition being extremely rare, it would almost be impossible to find young infertile patients with renal/hepatic insufficiencies.

Analytical Methodology

The sponsor, at our request, has submitted details of analytical methods, validation reports, and quality control reports. It appears that a standard "kit" assay method was used for the PK studies. All values for accuracy, precision and ruggedness range between ± 0 – 15%. This is acceptable, since some of the high % values correspond to low concentrations measured.

Labeling Comments

The "Pharmacokinetics" section of the label accompanying this application reflects results of older PK studies in women. The sponsor was requested to maintain the format, but update all the information (including the Table 1 in the label) from PK studies in men submitted with this supplemental application (study #s 5665 and 5826). The sponsor modified Table 1 accordingly, and incorporated the relevant information in this section satisfactorily. Hence, the modified label (version dated 5/11/2000) is acceptable from a Clinical Pharmacology and Biopharmaceutics standpoint.

APPENDIX I

Facsimile confirming no change in drug formulation

[illegible]

Confidential

[illegible]

September 1, 1999

Lisa Rarick, M.D., Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-378
Gonal-F® (follitropin alfa for injection)
General Correspondence:

Dear Dr. Rarick,

Reference is made to NDA 20-378 for Gonal-F® (follitropin alfa for injection) approved on September 29, 1997. Further reference is made to a supplement New Drug Application, S-006, submitted on July 26, 1999 which provided for revised labelling and clinical data to support a new indication: administration of Gonal-F® with concomitant chorionic gonadotropin for the stimulation of spermatogenesis in males with hypogonadotropic hypogonadism. Reference is also made to a telephone conversation between Ms. Eutrecinia DeGuia and D. DeMuria on August 11, 1999, whereby Serono was asked to submit in writing to the Division that the above referenced supplement does not provide a CMC change to either drug substance, drug product or drug strength as requested by Dr. Rhee.

Accordingly, this letter serves as written confirmation that Clinical Supplement S-006 provides for a labelling change only for the indication of male hypogonodotropic hypogonadism and does not provide for a change in formulation or any change to the chemistry or manufacturing of the drug substance or drug product.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267.

Yours sincerely,

Thomas A. Lang,
Senior Vice President, Regulatory Affairs

cc: Ms. E DeGuia, FDA (by fax)

APPENDIX 2

Pharmacokinetic Study Details for

- **Single Dose Study (5665) &**
- **Multiple Dose Study (5826)**
- **Bioequivalence Study (6570)**

vitro immunoradiometric assay (see 3.3.2). To allow computation of pharmacokinetic parameters, the concentration of FSH in the vials of the batches injected was also estimated by the same *in vitro* immunoradiometric assay used to assess FSH serum level.

3.3.1. *In vivo* bioassay

3.3.2. *In vitro* immunoassay

3.4. STUDY PROCEDURE

3.4.1. Single dose study Study 5665

The subjects were divided randomly into 2 groups of 6 subjects. The test drug (r-hFSH) and the control drug (u-hFSH) were administered subcutaneously according to a crossover design including a washout period of 3 weeks. The content of each 3 vials of 75 IU r-hFSH was dissolved in 0.5 mL of the attached solvent, and a total of 1.5 mL (225 IU) was administered with a plastic syringe (Terumo 2.5 mL) subcutaneously. The content of 3 ampoules of u-hFSH was dissolved in the attached solvent (0.5 mL of saline) and a total of 1.5 mL (225 IU) was administered in a similar manner as the test drug immediately after reconstitution.

3.4.2. Repeated dose study Study 5826

The content of 3 vials (225 IU) of r-hFSH was dissolved in a manner similar to the single administration study and administered subcutaneously to the subjects once a day for 7 days.

4.2. PHARMACOKINETICS

4.2.1. Single administration study

The contents of 75 IU vial of u-hFSH and of r-hFSH are shown in Table 8. Accordingly, the doses, as assessed by the *in vitro* immunoassay ——— used for the pharmacokinetic calculations were: 187.5 IU for u-hFSH and 150 IU for r-hFSH.

The raw data and the baseline subtracted concentrations (observed minus baseline) are presented in Appendix B. The mean baseline FSH concentrations were essentially the same in the two phases of the cross-over study. The baseline subtracted concentration vs. time plot are presented in Figs 8 and 9.

4.2.1.1. Non-compartmental analysis

The pharmacokinetics of FSH after baseline subtraction are presented in Appendix C and are summarised here below as mean ± 1 SD.

	C_{max} IU/L	t_{max} h	mean 0 IU/L	k_e h^{-1}	$t_{1/2}$ h	AUC IU·h/L	MRT h	CL/F L/h	V_z/F L
187.5 IU u-hFSH	7.5 ± 1.6	10 ± 2	4.1 ± 1.1	0.022 ± 0.010	39 ± 17	506 ± 125	64 ± 16	0.39 ± 0.09	25 ± 8
150 IU r-hFSH	2.5 ± 0.8	20 ± 14	4.4 ± 1.3	0.019 ± 0.007	41 ± 14	220 ± 109	77 ± 21	0.86 ± 0.48	59 ± 23

Study 5665

The FSH concentrations appear to be lower following the injection of r-hFSH than after u-hFSH: C_{max} is lower, and possibly delayed. As seen in Fig 10, the difference in serum concentration is not proportional to the difference in the administered doses. The AUC is larger after u-hFSH than after r-hFSH. The differences in C_{max} and AUC are similar between the two products. The apparent elimination half-life is, however, very close in the two formulations, especially after exclusion of the data from two volunteers who have extreme estimated k_e values (as in the above Table). MRT is also quite similar in the 2 phases, since the apparent volume of distribution varies in the same proportion as the apparent clearance.

4.2.1.2. One-compartment model analysis

After visual inspection of the baseline subtracted concentrations vs. time plots, three points (1 for AN05, two for AN09) were considered probable errors, and were not included in the subsequent non-linear regressions (see Appendix B). Moreover, the FSH concentration after r-hFSH administration showing only a limited increase compared to baseline values, fluctuations in the latter have a major contribution to the reduced concentrations so that the data are less dependable for this phase. The concentrations from only three subjects could be adequately fitted by the model in this phase (Appendix C). Conversely after u-hFSH injection, all subjects showed FSH concentrations well fitted by the model. Although the results after u-hFSH are in close agreement with those originated from the non-compartmental analysis, no

comparison between the preparations should be based on these curve fittings, since they are poorly reliable for r-hFSH.

4.1.2. Repeated administration study

The content of 75 IU vial of r-hFSH is presented in Table 9. Accordingly, the dose utilised for the pharmacokinetic calculations was 165.8 IU.

The raw data and the baseline subtracted concentrations are presented in Appendix D. The mean baseline FSH concentrations were 2.2 - 3.5 IU/L. In order to minimise the effect of baseline fluctuations during the 20 days of observation, when the "reduced" concentration was lower than two standard deviations of the corresponding baseline, its value was considered as missing for the curve fitting.

The mean baseline subtracted concentration vs. time plot is depicted in Fig 11. The individual pharmacokinetic parameters are presented in Appendix E and are summarised here below:

Pharmacokinetic parameters calculated after repeated administration of r-hFSH (Mean ± 1 SD)

fitted parameters			calculated parameters				single dose [a]		ss [b]
C(0)	λ_z	k_a	CL/f	$t_{1/2a}$	$t_{1/2}$	V/f	AUC	MRT	accumul.
IU/L	h^{-1}	h^{-1}	L/h	h	h	L	IU·h/L	h	ratio
4.9	0.022	0.134	0.90	5.3	32	42.1	186	54	2.5
(1.1)	(0.003)	(0.025)	(0.12)	(0.9)	(4)	(8.5)	(23)	(6)	(0.2)

Study 5826

[a] calculated as for one single dose
[b] steady state accumulation ratio

The results obtained after repeated SC administration of r-hFSH are in good agreement with the one obtained in the first group of 12 volunteers after single SC administration.

5. DISCUSSION

This Phase I study is designed to investigate the safety, the pharmacodynamics and the pharmacokinetics of a r-hFSH preparation in Japanese healthy male volunteers after single subcutaneous administration and after 7 daily subcutaneous administration. Recombinant hFSH is produced by a genetically engineered mammalian cell line (CHO) which have been cloned from the human genes encoding the α- and the β-subunits of FSH. Since it is a fully

Study 5665 (Single Dose)

Non-compartmental pharmacokinetic analysis

225 IU Fertinorm	Dose	187.5 IU u-hFSH							
Subject	C_{max}	T_{max}	mean 0	k_e	$t_{1/2}$	AUC	AUMC	MRT	CL/f	V_z/f
			IU/L			IU	IU h/L	h	L/h	
AN 1			5.11						0.50	
AN 2			5.23						0.46	
AN 3			5.50						0.42	
AN 4			4.53						0.35	
AN 5			4.77						0.24	
AN 6			2.83						0.61	
AN 7			4.67						0.40	
AN 8			3.67						0.43	
AN 9			2.03						0.36	
AN 10			4.90						0.34	
AN 11			3.07						0.33	
AN 12			5.00						0.45	
mean	[illegible]	10.3	4.1	0.022	37	506	33524	64	0.39	25
sd	5.5	1.9	1.1	0.010	17	125	16126	16	0.09	8
cv%	21%	18%	28%	46%	44%	25%	48%	24%	24%	31%

225 IU Gonal-F	Dose	150 IU r-hFSH							
Subject	C_{max}	T_{max}	mean 0	k_e	$t_{1/2}$	AUC	AUMC	MRT	CL/f	V_z/f
			IU/L						L/h	
AN 1			5.53						0.60	
AN 2			2.73						0.86	
AN 3			4.83						3.68	
AN 4			4.50						0.65	
AN 5			5.50						1.30	
AN 6			2.63						2.00	
AN 7			5.13						0.47	
AN 8			4.50						0.92	
AN 9			2.30						0.78	
AN 10			5.67						0.33	
AN 11			3.43						0.56	
AN 12			5.47						0.79	
mean	2.5	14.5	4.4	0.022	50	206	20473	97	1.08	72
sd	0.8	14.5	1.3	0.017	43	111	18246	57	0.93	38
cv%	32%	73%	29%	79%	86%	54%	89%	85%	86%	53%
without "outliers" (shaded)			mean	0.019	41	210	18675	77	0.86	59
			sd	0.007	14	109	14386	21	0.48	23
			cv%	38%	33%	49%	77%	28%	56%	39%

053

Study 5665
(Single Dose)

One-compartment model pharmacokinetic analysis

225 IU Fertinorm	Dose	188 IU u-hFSH							
Subject	V/f	k_a	λ_z	t_{lag}	$t_{1/2}$	AUC	AUMC	MRT	CL/f
	L	h^{-1}	h^{-1}	h	h	IU h/L	IU h^2/L	h	L/h
AN 1									0.28
AN 2									0.46
AN 3									0.40
AN 4									0.33
AN 5									0.29
AN 6									0.60
AN 7									0.38
AN 8									0.42
AN 9									0.42
AN 10									0.33
AN 11									0.33
AN 12									0.43
mean	31	0.35	0.020	0.6	39	[illegible]	[illegible]	[illegible]	0.39
sd	8	0.36	0.007	0.4	12	104	12552	15	0.09
cv%	37%	102%	36%	69%	32%	21%	40%	24%	23%

225 IU Gonal-F	Dose	150 IU r hFSH							
Subject	V/f	k_a	λ_z	t_{lag}	$t_{1/2}$	AUC	AUMC	MRT	CL/f
	L	h^{-1}	h^{-1}	h	h	IU h/L	IU h^2/L	h	L/h
AN 2									0.69
AN 7									0.35
AN 11									0.59
mean	42	0.13	0.016	1.5	47	301	25011	77	0.54
sd	8	0.07	0.006	1.9	18	114	17910	25	0.17
cv%	19%	57%	34%	128%	39%	38%	72%	33%	32%

054

Study 5826
(Multiple Dose)

Pharmacokinetic analysis

	fitted parameters			calculated parameters				single dose			ss
	C(0)	λ_z	k_a	V/f	$t_{1/2a}$	$t_{1/2}$	CL/f	AUC	AUMC	MRT	accumul.
Subject							L/h	IU·h/L	IU h²/L	h	ratio
AN 13							0.84				
AN 14							0.80				
AN 15							0.90				
AN 16							1.11				
AN 17							0.80				
AN 18							0.97				
mean	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0.90	186	10086	54	2.5
sd	1.1	0.003	0.025	8.5	0.9	4	0.12	23	1655	6	0.2
cv%	23%	15%	19%	20%	18%	13%	13%	12%	16%	10%	10%

	observed parameters			
	first dose		last dose	
	C_{max}	t_{max}	C_{max}	t_{max}
Subject	IU/L	h	IU/L	h
mean	2.8	9.3	8.3	[illegible]
sd	0.5	2.4	0.9	6.7
cv%	19%	26%	11%	62%

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Packages : Each box contains 10 vials of Gonal-F accompanied with 10 ampoules of solvent.

3.3. METHOD OF ADMINISTRATION AND DOSAGE

3.3.1. METHOD OF ADMINISTRATION

This was a bioequivalence study in 12 healthy male volunteers between 75 IU/vial and 150 IU/vial formulations of Gonal-F by subcutaneous administrations. Subjects were allocated into two groups using a Latin square design. Each subject was subcutaneously administered either 4 vials of Gonal-F (75 IU/vial) or 2 vials of Gonal-F (150 IU/vial) which were reconstituted with 2.0 ml of Water for Injection (Step 1). Three weeks later, the test drugs were switched according to a cross-over method (Step 2). Gonal-F was injected immediately after reconstitution.

3.3.2 DOSAGE

Gonal-F at 300 IU/injection

No. of Subject	Step 1	Step 2
No. 1~6	Gonal-F (75 IU/vial) x4	Gonal-F (150 IU/vial) x2
No. 7~12	Gonal-F (150 IU/vial) x2	Gonal-F (75 IU/vial) x4

BF Study 6570

3.4 OBSERVATION ITEMS AND LABORATORY TESTS

Pre-study examination items are summarized in Table 2. The following items were observed or examined according to the schedule shown in Table 3 for the study.

(1)Medical examination
(2)Subjective symptoms
(3)Blood pressure and heart rate
(4)Body temperature
(5)12-lead ECG
(6)Hematological examinations : White blood cell count, red blood cell count, hemoglobin concentration, hematocrit value, platelet count and differential white blood cell
(7)Blood biochemical examinations : Total bilirubin, direct bilirubin, GOT, GPT, ALP, LDH, γ-GTP, Ch-E, total protein, albumin, A/G, protein fraction, BUN, uric acid, creatinine, total cholesterol, triglyceride, glucose, Ca,

Study 6570

Table 10 : Pharmacokinetic parameters (Reduced values)

	75 IU/vial	150 IU/vial
AUC (h·mIU/ml)	312 ± 51	328 ± 92
C_{max} (mIU/ml)	3.25 ± 0.65	3.70 ± 1.53
t_{max} (h)	32.0 ± 11.8	28.8 ± 12.2

n=12, Mean±SD

Table 11 : ANOVA of C_{max} (Reduced values)

Source of Variance	Degrees of Freedum	Sum of Squares	Mean Squares	(F)	Test
Between Subjects	11	21.4	1.94	2.14	N.S
Group or Sequence	1	2.12	2.12	1.10	N.S
Subjects/Group	10	19.2	1.92	2.12	N.S
Within Subject					
Drugs	1	1.23	1.23	1.36	N.S
Time Periods	1	0.0000666	0.0000666	0.00007	N.S
Residual	10	9.06	0.906		
Total	23	31.7			

F0.1 (1,10) = 3.29 :F0 05 (10,10) = 2.98 :F0.05 (1,10) = 4.96

Difference in average values = 13.96 %

Power (1− β) = 32.8 % :Minimum detection difference (Δ) = 37.2 %

95 % confidence limit = −12.7~40.6 %

Table 12 Analytical results of AUC (Reduced values)

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Squares	(F)	Test
Between Subjects	11	94700	8610	4.39	1.35 %
Group or Sequence	1	4920	4920	0.548	N.S
Subjects/Group	10	89800	8980	4.57	1.23 %
Within Subject					
Drugs	1	1530	1530	0.778	N.S
Time Periods	1	6930	6930	3.53	N.S
Residual	10	19600	1960		
Total	23	123000			

F0.1 (1,10) = 3.29 :F0.05 10,10) = 2.98 :F0.05 (1,10) = 4.96

Difference in average values = 5.11 %

Power (1− β) = 87.4 % :Minimum detection difference (Δ) = 18.0 %

95 % confidence limit = −7.8~18.0 %

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Study 6570

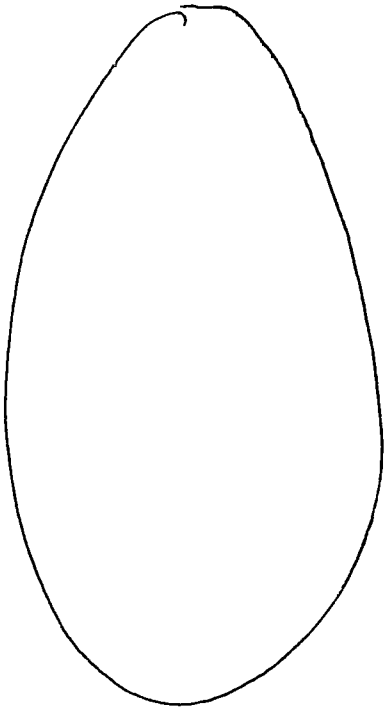

Fig 4 Serum FSH concentration following administration (Observed values)

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APPENDIX 3

Results confirming no gender/race differences in PK

Confidential

2. The pharmacokinetic (PK) studies were conducted in Japanese men. However, no information comparing PK between males and females or among ethnic groups was provided in the application. Therefore we ask that you send us the following:

a. a compilation of data comparing key PK parameters in all racial groups in which Gonal-F® was administered; and

b. a compilation of data comparing key parameters in males and females (since Gonal-F® is currently approved for a female indication only)

Serono has performed a series of pharmacokinetic studies in healthy volunteers after administration of Gonal-F® to Asian males (Study GF 5665 and Study GF 5826), to Asian females (Study 20493) and to Caucasian females (Study GF 5117 and Study 20484). To the question regarding potential ethnic differences (a), a Wilcoxon test was performed when relevant. To the question related to potential gender differences (b), we refer to compiled data. As it is further demonstrated, based on these studies, there is no evidence to support any pharmacokinetic differences between genders or between ethnicities. Study reports are included in Attachments VII and VIII:

Attachment VII: Study 20484: "*A Phase I Study to Assess the Pharmacokinetics and the Safety of Recombinant-human Follicle Stimulating Hormone (Gonal-F®) After Single Subcutaneous Administration in Caucasian Healthy Premenopausal, Down-Regulated Female Volunteers*"

Attachment VIII: Study 20493: "*Pharmacokinetic Study with SJ-0021 in Healthy Female Volunteer s After Single Administration*"

Although these studies were performed at different times, by different centers and FSH was measured by 2 different methods (——— immunoassay in Study GF5117, Study 5665 and Study 5826; and —— immunoradiometric assay in Study 20484 and 20493), data were compiled across studies. Since there were some differences between experimental conditions, and given the small number of patients per study, the use of tables and descriptive graphs was considered more relevant and meaningful than comparisons based on hypothesis testing. Summary statistics for AUC, C_{max}, t_{max}, $t_{½}$, CL/F and R are listed in Tables 2 to 7, with boxplots.

Overall, as evidenced by the boxplots, all pharmacokinetic parameters compared well across studies, males or females, Caucasian or Asian. Half-life was generally estimated around 26 hours for both males and females. T_{max} compared well across genders although a slightly longer median t_{max} (24 h) was obtained in Study 20484; which might be due to the absence of sampling time points between 15 h and 24 h. The mean apparent clearance ranged from 0.6 to 0.9 L/h across all studies, and was very similar in females and in males, around 0.8 L/h in and 0.9 L/h, respectively. (This is felt to be the most important parameter to compare since it is the reciprocal of the dose-normalized exposure) Renal clearance represented consistently a small part of the apparent clearance (overall less than 8%). The apparent

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Table 3: C_{max} (IU) as Estimated from the Immunoassay Data of 5 Phase I Studies After Single or Repeated Injections of Gonal-F®

Study	GF5665	GF5826	IMP20493		GF5117		IMP20484
Race	Asian	Asian	Asian		Caucasian		Caucasian
Number of subjects	12	6	6	6	12		6
Sex	Male	Male	Female	Female	Female		Female
Route of administration	SC	SC	SC	SC	SC	SC	SC
Daily FSH nominal dose (IU)	225	225	150	300	150	150	300
# of daily injections/total # injections	1/1	1/7	1/1	1/1	1/1	1/7	1/1
Mean	**2.5**	**8.3**	**3.3**	**7.7**	**3.2**	**8.8**	**7.5**
Standard deviation	0 8	0 9	1.0	0.9	0 9	2.8	0 9
Median	2.3	8.4	3.4	7.7	3.2	9.6	7.2
Median absolute deviation	0.5	1.0	1.0	1.0	0.8	2.4	0 9
Min	1.6	7.2	1.7	6.3	2.0	3.5	6 6
Max	4.4	9.5	4.4	8.6	4.8	11.8	8 7

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Table 5: Half-life (h) as Estimated from the immunoassay Data of 5 Phase I Studies After Single or Repeated Injections of Gonal-F®

Study	GF5665	GF5826	IMP20493		GF5117		IMP20654
Race	Asian	Asian	Asian		Caucasian (n=12)		Caucasian
Number of subjects	12	6	6	6	12		5
Sex	Male	Male	Female	Female	Female		Female
Route of administration	SC	SC	SC	SC	SC	SC	SC
Daily FSH nominal dose (IU)	225	225	150	300	150	150	300
# of daily injections/total # injections	1/1	1/7	1/1	1/1	1/1	1/7	1/1
Mean	**41.5**	**32.2**	**28.9**	**25.3**	**24.0**	**23.6**	**26.3**
Standard deviation	13.9	4.2	8.5	3.3	10.5	8.1	3.5
Median	40.0	33.2	27.6	24.3	26.6	24.4	26.6
Median absolute deviation	15.8	4.0	8.6	2.9	10.7	8.3	4.4
Min	20.0	25.1	20.9	21.9	8.1	10.6	22.6
Max	63.6	36.9	43.5	29.6	37.2	36.7	31.6

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Table 6: Apparent Clearance (L/h) as Estimated from the Immunoassay Data of 5 Phase I Studies After Single or Repeated Injections of Gonal-F®

Study	GF5665	GF5826	IMP20493		GF5117		IMP20484
Race	Asian	Asian	Asian		Caucasian (n=12)		Caucasian
Number of subjects	12	6	6	6	12		5
Sex	Male	Male	Female	Female	Female		Female
Route of administration	SC	SC	SC	SC	SC	SC	SC
Daily FSH nominal dose (IU)	225	225	150	300	150	150	300
# of daily injections/total # injections	1/1	1/7	1/1	1/1	1/1	1/7	1/1
Mean	**0.9**	**0.9**	**0.8**	**0.6**	**0.8**	**0.6**	**0.6**
Standard deviation	0.5	0.1	0 3	0.1	0.3	0.1	0.1
Median	0.8	0.9	0.7	0 6	0.7	0.6	0.6
Median absolute deviation	0.3	0.1	0.2	0.1	0.2	0.1	0 1
Min	0 3	0.8	0.5	0.4	0.5	0 4	0 5
Max	2.0	1.1	1.4	0.7	1.4	0 7	0.7

Deguia

Review and Evaluation of Pharmacology/Toxicology Data

APR - 3 2000

HFD-580/Karen Davis-Bruno; Ph.D.

Supplemental NDA 20-378
Serono Laboratories, Inc.

Submission Date: 7/27/99

Gonal-F (r-hFSHα; follitropin alpha for injection)

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NDA 20-378
Cc: HFD-580/Davis-Bruno/Jordan/Deguia

Supplemental NDA 20-378
Serono Laboratories, Inc.

Review and Evaluation of Pharmacology/Toxicology Data
Key Words: recombinant human follitropin alpha, FSH, IVF, ART
Karen Davis-Bruno; Ph.D.
Division of Reproductive and Urologic Drug Products/HFD-580
Review completion date: 1/24/00

NDA 20-378 Supplement #006
Type of Submission: supplemental NDA 7/27/99
Information to Sponsor: Yes ( ), No (X)
Sponsor: Serono Laboratories, Norwell, MA
Manufacturer: Laboratoires Serono SA; Aubonne, Switzerland

Drug:

Code Name: r-hFSHα

Generic Name: recombinant human follitropin α; follicle stimulating hormone

Trade Name: Gonal-F

Structure: r-hFSH is a human glycoprotein hormone consisting of two non-covalently linked non-identical protein components designated as α and β. The α subunit consists of 92 amino acids [redacted] The β subunit consists of 111 amino acids [redacted]. R-hFSH is derived from a Chinese Hamster Ovary cell line which has been transfected with human genes that encode for the α and β subunits of FSH.

Relevant IND/NDAs: NDA 20-378, IND 38,712
Other FSH preparations by Serono include: NDA 17-646 for Pergonal (metropins hMG; equal FSH: LH) and NDA 19-415 for Metrodin (urofollitropin: purified hMG to remove LH), Metrodin HP(urofollitropin for injection, IND [redacted].

Drug Class: recombinant pituitary gonadotropin

Indication: induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in combination with hCG for initiation and re-initiation of spermatogenesis.
Advantages of Gonal-F cited by the sponsor:
1. alternative to menopausal gonadotropin preparations, absence of urinary derived protein contamination
2. reliable, safe source of gonadotropins
3. absence of LH activity

Clinical Dose: Recommended dose is 150 IU, 3X/week, SC for at least 4 months (usually effective within 6-8 months). The sponsor suggests that doses up to 300 IU/day may be used up to 18 months. Pretreatment with h-CG (1000 U, 3X/week) is required.

Drug Product: human recombinant DNA preparation of FSH approved (NDA 20-378) for induction of follicular development and ovulation in women with oligo-anovulatory infertility and multiple follicular development in women undergoing assisted reproductive technology (ART) procedures e.g. in vitro fertilization (IVF)/embryo transfer (IVET).

Formulation: Each Gonal-F vial contains 75 IU or 150 IU [redacted]
30 mg sucrose, [redacted]
[redacted] Gonal-F is reconstituted in sterile water for injection.

Route: subcutaneous

Drug History: Serono was given an orphan designation for Gonal-F for male hypogonadal hypogonadism (HH) on 10/98 and obtained approval of a supplemental NDA on 12/98. Gonal-F has been approved for the treatment of male HH by the European Union and Argentina.

HH is a rare, heterogeneous disorder of reproductive function characterized by azoospermia in the presence of low serum gonadotropin and testosterone levels. Replacement of LH for normalization of intratesticular testosterone and FSH for stimulation of spermatogenesis is recommended. FSH has been administered as menotropins (Pergonal; human menopausal gonadotropins containing LH:FSH at 1:1). The primary effect of menotropins are understood to be through its FSH content. Menotropins administered concomitantly with hCG have been used effectively for 30 years. Usual treatment of men with HH for infertility begins with hCG administration to induce androgenization of seminiferous epithelium followed by direct stimulation of the epithelium with FSH.

Three Phase III multicenter trials (Studies 5844, 6410, 6793) were performed with starting doses of 150 IU, SC given every other day for a maximum of 18 months of treatment. Dose escalations were recommended if patients remained azoospermic or were not achieving satisfactory sperm levels. In three studies, 69.2-81.8% of patients achieved spermatogenesis and 46.2-63.6% achieved a sperm density of $\geq$ 1.5E6/ml, a density associated with a high probability of fertility (primary endpoint). Patients also demonstrated an increase in testicular volume, a key measure of FSH effect. The sponsor reports that in studies 5844 and 6410 anti-FSH antibodies were not observed. The interim analysis of study 6793 will be provided in the final study report. The sponsor's table of completed clinical trials attached to this review.

Most preclinical studies pertaining to this supplemental NDA have been reviewed under IND 38, 712 (1/24/92, 6/3/93, 10/22/93) and NDA 20-378 (9/10/93).
Pharmacology: The physiochemical, immunological and biological activities of r-hFSH are noted as similar to those of human menopausal, urine derived FSH according to the sponsor.

In males with hypogonadotropic hypogonadism (lack or deficiency in GnRH) gonadotropin therapy can be used to restore fertility with prolonged treatment. Germinal maturation in the tubules requires 10 weeks and the transit of spermatozoa through the

vas deferens several weeks more. Treatment is initiated with 5000 IU of CG intramuscularly 3X/week to stimulate testosterone production. HMG therapy to stimulate the FSH-dependent process of spermatogenesis is then initiated at 75 IU of FSH and 75 IU of LH activity given intramuscularly 3X/week and the dose of CG is decreased to 2000 IU 2X/week. Maturation of the pre-pubertal testes requires treatment for 3-6 months with high LH/FSH ratios. Once spermatogenesis has been initiated by this combined therapy, CG alone usually can be administered to maintain sperm production. Optimal spermatogenesis may require gonadotropin therapy for 12 months.

The sponsor has not performed pharmacology studies for the male indication, but instead provides summaries of related literature reports.

1) [Endocrinology 1995; 136: (9)4035-4043]- r-hFSH partially restores spermatogenesis in gonadotropin-deficient rats by increasing spermatogonia and promoting maturational steps up to the round spermatid stage. Spermatid elongation was not restored indicating the need for additional treatment.
2) [Endocrinology 1995; 136: 253-261]- r-hFSH aids in maintenance of spermatogenesis in the adult rat
3) [Biol. Reprod. 1996; 54:36-44]- r-hFSH treatment of neonatal rats results in testicular hypertrophy, increases in seminiferous tubule volume, length and proportional increases in Sertoli and germ cell numbers. The effects continued into adulthood.
4) [J Endocrinology 1995; 147:463-471; J. Physiol. Biochem. 1997; 53: (3)289-300]- Testicular macrophages are required for the response of Leydig cells to gonadotropin treatment
5) [Andrologia 1997; 29:85-90]- The response of atrophic Leydig cells to gonadotropin supplementation was partially inhibited in the presence of GnRH antagonist.

Safety Pharmacology: Neurobehavioral effects; including temperature, anticonvulsant and analgesic activities were evaluated in mice given up to 500 IU/kg, SC without an apparent CNS effect. No significant effect on intestinal motility in mice was observed using doses up to 500 IU/kg, SC followed by a charcoal meal. In vitro studies in isolated guinea pig ileum demonstrate that r-hFSH had no effect on the force of contractions induced by test compounds when given up to 0.50 IU/ml in an organ bath. Treatment of dogs (IV) at doses up to 500 IU/kg had no effect on hemodynamic, cardiac and respiratory rate parameters. Occasional difference in BP and HR were observed but were not dose related and therefore not considered significant.

Pharmacokinetics:

Single SC Dose	Rat (10 IU/kg)	Monkey (10 IU/kg)	Human (2.4 IU/kg)
Cmax (IU/L)	21	16±7	3±1
tmax (h)	4-12	7±2	14±7
t1/2 terminal (h)	14	21±3	37±28
$AUC_{0-\infty}$ (IU h/L)	610	600±200	235±144

Repeat SC Dose	Rat (10 IU/kg) Dose 14	Monkey (10 IU/kg) Dose 7	Human (2.4 IU/kg) Dose 7
Cmax (IU/L)	17	33±4	9±3
tmax (h)	6	150±2	8±6
t1/2 terminal (h)	14	21±2	24±8
$AUC_{144-168}$ (IU h/L)	296	570±60	187±61

Means represent combined sexes since there was no difference between sexes. The plasma profile of pregnant rats was similar to non-gravid rats. The reduction in AUC with repeated dose administration could be a result of neutralizing antibodies. The PK profile in monkeys after single and repeated dose was similar with a 2X accumulation factor between the first and seventh dose.

Human PK:

Gonal-F and Metrodin have very similar PK in vivo. The absolute bioavailability of r-hFSH following repeated IM or SC administration was ~70% by immunoassay. The PK of r-hFSH appeared linear following repeated SC administration when assayed by immunoassay. The t1/2 was ~1 day with an accumulation factor of ~3 when steady state was reached in 3-4 days.

Toxicology:

Acute: Acute oral dosing of rats at 10,000 IU/kg had no reported effects on general behavior, body weight or gross pathology. A single dose study in rats given r-h-FSH at 1000, 2000, 4000 IU/kg by IV, IM, and SC routes was performed. Rats were evaluated at 14 days post dose no adverse effect was noted. A single dose IV (200 IU/kg) study was performed in dog with an evaluation at 14 days post dose. One female dog had transient hypersalivation and one male vomited on dosing and on Day 10. Dogs treated with u-hFSH had slight, transient increase in SGPT, 48 h after injection which returned to baseline on Day 15. Histopathology findings were not present.

Monkeys were given a single IV, SC or IM dose of 2000 IU/kg without adverse events. Following a one week washout a single dose of 4000 IU/kg was given. Necropsy revealed no drug related changes in males but in females ovarian volume increased and hemorrhagic follicles were found in those given r-hFSH by IV route. Hemorrhages in the uterine lumen of females treated by SC and IM routes were observed. Histology revealed ovarian follicle cysts and atrophy of corpora lutea in all females and a unilateral moderated follicular hematocytst in the female treated by IM route. Endometrial hemorrhages with degeneration were reported in animals treated by SC and IM routes and endometrial hypertrophy were observed in monkeys treated by IV route. These changes were attributed to the pharmacologic activity of r-hFSH and except for the follicular hematocyst, seen in normal cycling monkeys according to the sponsor.

Single Dose Finding Adult Male Monkey Study

Study No. GF 5467
Date: 12/2/91-4/2/92
Species: Macaca fascicularis (cynomolgus monkey)
Weight: 4.7-6.9 kg
#/sex/group: 5 males/group
Lot: 19506101, 150 IU/vial
Vehicle: saline
Route: IM injection
Dose: single @ 6, 12, 24 IU/kg of R-hFSH or 24 IU/kg U-hFSH (Metrodin 150 IU/vial lot #07506101) dose was determined according to in vivo bioactivity units determined by rat in vivo ovarian weight gain assay.

Methods: blood collected at 4, 8, 12, 24, 72 and 96 h post dose for PK and immunoassay (DELFIA immunoassay) determinations. Serum inhibin was quantified as a marker for FSH stimulation of Sertoli cell function and to estimate a daily dose of r-hFSH needed to restore/stimulate spermatogenesis in men.

Pharmaco-kinetics	R-hFSH (6 IU/kg)	R-hFSH (12 IU/kg)	R-hFSH (24 IU/kg)	U-hFSH (24 IU/kg)
Immuno-activity (IU/kg)	2	4	8	14
Tmax (h)	9±3	5±2	6±2	4±0
T ½ terminal	22±4	18±4	22±5	20±5
$AUC_{0-\infty}$ (IU h/L)	223±11	322±72	818±207	1646±293
Cmax (IU/l)	5.5±1.3	11.5±1.4	23±7	54±17

Serum Inhibin responses	R-hFSH (diluent)	R-hFSH (6 IU/kg)	R-hFSH (12 IU/kg)	R-hFSH (24 IU/kg)	U-hFSH (24 IU/kg)
Baseline inhibin (U/l)	3776±404	4254±420	3632±420	2751±414	2673±269
$AUC_{0-\infty}$ $^{+}$ ($IUX10^{3}$ h/l)	14±9	16±2	35±7	50±12*	73±8*
Tmax (IU/l)	-	1.7±0.7	2.1±0.6	2.2±0.8	1.3±0.3

$^{+}$area under FSH curve

The intra-assay coefficient of variation (CV) was 4.2% and the inter-assay CV was 5.1% for serum inhibin (J. Endoc. (1989)122:477-483).

Neither R-hFSH nor U-hFSH had any discernible effect on levels of circulating testosterone. A dose related stimulatory effect of R-hFSH on serum inhibin was evident, which was statistically significant only in the 24 IU/kg of R-hFSH or U-hFSH but no difference between monkeys receiving the recombinant or Metrodin.

Key Study Findings: R-hFSH stimulates Sertoli cell function in monkey with a dose range similar to Metrodin (U-hFSH). The pharmacokinetic properties of R-hFSH are similar to Metrodin. The long serum T1/2 suggests that injection every 2-3 days may be sufficient for providing continuous FSH stimulation for Sertoli cell functions that regulate spermatogenesis.

Subchronic: One month studies in rats given 10, 30, 100 IU/kg/day r-hFSH SC or 100 IU/kg/day u-hFSH, revealed slight acinar hyperplasia of the mammary gland in some LD females and perivascular mononuclear cell cuffing sometimes associated with inflammation and hemorrhage at the injection site. Higher doses revealed reductions in partial thromboplastin time in treated males compared to controls. Ovarian weight was significantly increased in HD females. Mid and High dose groups had corpora lutea atrophy associated with follicle cyst and/or increase in follicle number, uterine atrophy with vaginal mucification and in some females mammary gland acinar hyperplasia. At the injection site mononuclear cell cuffing sometimes with inflammation and hemorrhage was seen in some females at a higher incidence than in controls. The histopathology noted was seen more frequently and of higher severity in the u-hFSH group. Reversibility of drug effects was evident although the PTT values were still decreased in HD males with some corpora lutea atrophy, vaginal mucification and acinar mammary

gland hyperplasia in MD and HD females was still observed after a one month recovery. There were no significant difference between r-hFSH and u-hFSH in this regard. All animals treated with 100 IU/kg/day had anti-h-FSH antibodies at the end of treatment and recovery. Some animals had undetectable serum levels of FSH 24 h after the last dose, a likely result of neutralizing antibody generation.

A one month IV dog study with 20, 100 IU/kg/day showed a dose related increase in ovarian, uterus, testes and prostate weight in treated animals. Slight to severe increases of follicular cysts associated with slight to moderate follicular granulosa cell vacuolation appeared dose related. High dose dogs had follicular hemorrhage. Slight to moderate dose related incidence/severity of hypertrophy with endometrial gland hyperplasia, sometimes accompanied by dilation were observed in all drug groups. Slight to moderate mucosal hypertrophy with hyperkeratosis was observed in all 100 IU/kg/day group dogs. Centrilobular acute inflammation was observed in HD dogs. Antibodies formed within 2 weeks of treatment.

A one month IM monkey study with doses of 10, 30, 100 IU/kg/day r-hFSH was performed. Testes and ovarian weight was increased in all treated animals. Ovaries contained cysts and the mid and high dose groups had increased uterine weights. At the end of recovery the only increase that remained was the testes of HD males. Ovarian changes consisted of follicular cysts associated with hematocysts, corpora lutea atrophy and decrease in the number of oocytes. Testicular changes consisted of an increase in the number of spermatozoa associated sometimes with an increase in tubular diameter. Mammary gland acinar hyperplasia was seen frequently in MD and HD groups. Hypertrophy of acidophilic pituitary cells in all females of the mid and high dose group and in one control female was observed. The changes in ovaries and testes are ascribed to FSH stimulation and subsequent estrogen production resulting in uterine, mammary and pituitary gland changes. Treatment effects were still present following recovery in the ovaries of FSH treated groups and testicular changes in the u-hFSH group. Antibodies were present, independent of dose in 3/11 males and 5/11 females by the fourth week of dosing. Muscle degeneration and/or inflammation (sometimes associated with hemorrhage) was seen more frequently at the injection sites of FSH treated animals.

An additional study in monkeys using 300, 1000 IU/kg/day, IM for one month revealed similar findings. The high dose caused persistent swelling of the external genitalia, which resolved during the two week recovery period. Increased ovarian and testicular weight with a decrease in thymic weight was observed. Increased ovarian follicles and degeneration of the corpus luteum and thymic atrophy correspond to the changes in organ weight. These changes were not reversible. The thymic changes may result from the high steroid production stimulated by FSH. Thymic involution is observed during sexual maturation (elevated steroid levels). Acinar hyperplasia of the mammary gland was considered secondary to profound ovarian estrogenic stimulation. Subacute inflammation was observed at the injection site and circulating antibodies for FSH were found in all treated groups from Day 15.

One month SC dosing in rats at 300, 1000 μg/kg/day followed by a two week recovery was performed. Body weight was decreased in males and increased in HD females. Food consumption decreased in males but remained unchanged in females. In females a decrease in mean ovarian and uterine weight was noted in the HD group with atrophy of the corpus luteum and uterus, ovarian follicle cysts, degeneration of vaginal

mucosa and hyperplasia of mammary gland acini. The decrease in weight of ovaries and uterus in rats was unexpected and may relate to inhibin production as well as inactiviation of the exogenous FSH by high levels of neutralizing antibodies which were at higher levels than that detected in monkeys (data not provided). Histopathology findings were not present in males. In general findings were greatly attenuated with r-hFSH compared to groups treated with hMG. Findings are consistent with the pharmacologic activity and since hMG contains both FSH and LH the u-hFSH groups would be expected to have exaggerated female reproductive effects. The sponsor states that 1000 µg/kg/day of r-FSH could activate the rat immune system such that it manages to neutralize FSH completely within 24 h of the dose. All rats had developed h-FSH antibodies within one month of dosing.

Chronic: Rats (males) received 10, 100, 1000 IU/kg/day by SC injection for one year. A dose related decrease in weight and size of testes was observed at doses ≥100 IU/kg. This may relate to inactivation of exogenous FSH by high levels of antibodies, receptor desensitization or inhibin production. An increase in frequency/severity of immature sperm in the epididymal tubules compared to controls, may indicate increased turnover of the germinal epithelium of the testes. Antibodies to FSH were detected in all animals receiving r-hFSH after 26 weeks. There were no differences in testosterone levels among groups. Detectable serum FSH levels 24 h after the last dose were noted in 4/12, 2/12, 2/12 rats in the LD, MD, HD groups, respectively, suggesting circulating neutralizing antibodies were present. Undetectable levels of FSH were present in 8/12, 10/12, 10/12 rats respectively.

Cynomologous male monkeys received daily IM injections of 10, 100, 1000 IU/kg/day for one year. A dose related increase in testicular volume was noted with time, in contrast to the rat. The increase in testicular volume occurred after one month dosing at the high dose, after 1-2 months at the mid dose and after 3-8 months at the low dose. Tubular dilation in all the HD and one of the MD animals was generally associated with an increased amount of lumen fluid, with the corresponding histology. A slight increase in the number of spermatozoa was observed in 2/4 animals in the HD group. Antibodies to human FSH were detectable in 4/4, ¾, ¾ monkeys in the LD, MD, HD groups, respectively after 52 weeks of treatment. Differences in testosterone levels and treatment related renal immunocomplexes were not observed.

Carcinogenicity: the sponsor requested a waiver for these studies under the approved female indication using the following rationale for support:

1. Mutagenicity studies were negative.
2. The active substance is a human derived protein (recombinant protein) that exhibits structural and pharmacological properties equivalent to its native counterpart and thus is not expected to possess carcinogenic properties.
3. Essential the product indication is for replacement therapy
4. The formation of neutralizing antibodies precludes studies of long duration in animals, this is particularly relevant in rodents, commonly used to carcinogenicity studies.

Reproductive Toxicology: A Segment I fertility study in rats given 5, 40, 3220 IU/kg/day SC for 60 days prior to mating in males and in females 14 days prior to mating to Gestation Day 7 revealed estrus irregularity in females. This required longer time for

copulation with reduced fertility. A 60% increase in the number of corpora lutea in the 40 IU/kg/day group without an increase in the number of implantations and some increase in pre and post implantation resorption. No fetal abnormalities were seen following cesarean section on Gestation Day 20. High dose males had a small decrease in testicular weight without histopathology changes. R-hFSH at 5 IU/kg/day was considered a NOEL.

A rabbit Segment II study with r-hFSH given 5, 40, 320 IU/kg/day SC from days 6-18 of gestation resulted in total loss of all fetuses after implantation except for two rabbits in the low dose group that spontaneously aborted on Day 22 and 23. Dams had large ovaries with developing follicles and many cysts and degenerate corpora lutea. Rh-FSH caused fetal death, toxicity and dystocia in both rats and more severely in rabbits, however teratogenic effects were not observed.

R-hFSH administered at 5, 40, 320 IU/kg, SC compared to 320 IU/kg h-MG during rat organogenesis (Gestation Day 6-17; Segment II) revealed difficult and prolonged parturition at 40 IU/kg/day (3/25) and 320 IU/kg/day (4/25), resulting in the death of one HD female. A lower body weight gain was seen in HD females at the end of gestation. A dose related increase in corpus luteum, pre-and post-implantation losses, resorptions and ovarian weight was found at doses ≥40 IU/kg/day on Gestation Day 20. Litters allowed to deliver provide a dose related number of still born pups, post implantation losses and lower numbers of live births at doses ≥40 IU/kg/day. No significant effects in the morphological, physical and behavioral development of F1 pups, except for the advanced time of appearance of some developmental landmarks in pups of the 320 IU/kg/day groups, attributed to the longer gestation period observed in this group. Females did not deliver in the hMG group. Observations were similar to those seen with r-FSH; increased number of corpora lutea, early resorptions, pre-implantation losses and increased ovarian weight. A slight increase in fetal anomalies represented by retarded skeletal ossification of head bones was noted in the hMG group.

A rat segment III study (treatment Gestation Day 15-Lactation Day 21) at the same doses (5, 40, 320 IU/kg/day SC) reveals dystocia in all pregnant HD females. Only 1/25 females had live pups, 7/25 had dead and macerated pups, 13/25 had all stillborn pups, 7/25 females in the HD group died due to dystocia. In the h-MG treated group, 7/19 had dystocia, none of the females were able to deliver and 4/19 died due to dystocia. Doses of 40 IU/kg/day increased ovarian weight females and is considered a maternal and developmental NOEL by the sponsor. The altered reproductive physiology in HD groups is expected due to the massive surge in estrogen and androgens and likely large increase in progesterone. The reproductive effects in animals were considered clinically irrelevant by the sponsor because 1) clinical doses are much lower and 2) r-hFSH is not intended for use during pregnancy.

Genetic Toxicology: Bacterial mutagenicity with standard salmonella Typhimurium and E. coli strains as well as mammalian mutagenicity in V79 Chinese hamster lung cells show negative results. Chromosome aberrations in cultured human lymphocytes and *in vivo* mouse micronucleus test demonstrate that r-hFSH is devoid of clastogenic effects.

Special Toxicity: A local tolerance study in rabbits (SC, IM) at 600 IU/kg demonstrates slight to moderate dose related muscle fiber degeneration with inflammation in some and

slight interstitial hemorrhage at the IM injection site at 24 h. These changes were not observed at 72 h or in controls or with SC dosing.

A sensitization test in guinea pigs comparing r-hFSH with metrodin (hMG, u-hFSH) using an intradermal route at the first challenge, resulted in 4/20 animals with slight skin erythema. At the second challenge the incidence increased to 4/8 animals with the same severity. The intensity and incidence of reaction was higher in the metrodin groups where 19/20 reacted on first challenge and all guinea pigs on the second challenge were positive. Edema was observed in all metrodin treated guinea pigs.

Overall Summary/Evaluation: The physicochemical, immunological and biological activities of r-hFSH are similar to those of human menopausal, urine derived FSH. Single and chronic toxicity studies in rat, dog and monkey, reprotoxicity testing (Segment I-III in rat and Segment II in rabbits), genotoxicity testing, local tolerance/sensitization in the rabbit and guinea pig have demonstrated that r-hFSH has a similar toxicity profile as u-hFSH, both have been tested clinically. The observed toxicity relates to excessive gonadal stimulation, which regresses in a few weeks following withdrawal of the drug treatment. The generation of neutralizing antibodies against FSH or delayed type hypersensitivity was found after administration of r-hFSH or u-hMG to animals. These findings were considered clinically irrelevant due to the human origin of the recombinant drug product. Furthermore, clinical experience with u-hMG fails to demonstrate adverse findings related to neutralizing antibodies.

Conclusions:

Preclinical and clinical data has shown that Gonal-F is safe and has an efficacy and safety profile similar to that of Metrodin (u-hMG, u-hFSH), which is approved. Pharmacology considers Gonal-F safe and recommends approval for the induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in combination with hCG for initiation and re-initiation of spermatogenesis.

Labeling Review: Label has been reviewed and is acceptable by Pharmacology.

Recommendations: Pharmacology recommends approval of Gonal-F for induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism in combination with hCG for initiation and re-initiation of spermatogenesis.

Recommendations to Sponsor: none

Reviewer/Team Leader Signature:

/S/

Cc: HFD-580 file/Davis-Bruno/Jordan/Bennett/Deguia

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Serono Laboratories, Inc.

Chemistry, Manufacturing and Controls

No review required.

EER

This section is not applicable. Chemistry review was not required.

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Serono Laboratories, Inc.

Microbiology Review

No microbiology review is required for this application.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 02, 2000

FROM: Eufrecina DeGuia
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (DRUDP); HFD-580
Office of Drug Evaluation III

EDe Guia

SUBJECT: Draft Labeling for NDA 20-378/S-006 Gonal-F (follitropin alfa for injection)

TO: File

Comment: The draft label which contained the Division's recommended changes was sent to Serono Laboratories via email (with password protection) and facsimile. The sponsor was instructed that all the words with single strikethrough need to be deleted and the words that are bolded and underlined need to be added.

The sponsor confirmed receipt of the label also on May 2, 2000.

cc:
HFD-580/Division File
HFD-580/EDeGuia

DeGuia

NDA 20-378/S-006

OCT 21 1999

Serono Laboratories, Inc.
Attention: Thomas Lang
Senior Vice President, Regulatory Affairs
100 Longwater Circle
Norwell, MA 02061

To DFS

Dear Mr. Lang:

Please refer to your July 27, 1999 supplemental new drug application for Gonal-F (follitropin alfa for injection).

We are reviewing the Clinical Pharmacology and Biopharmaceutics section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your supplemental application.

1. Please submit the analytical method validation reports for review.

2. The pharmacokinetic (PK) studies were conducted in Japanese men. However, no information comparing PK between males and females or among ethnic groups was provided in the application. Therefore we ask that you send us the following:

   a. a compilation of data comparing key PK parameters in all racial groups in which Gonal-F was administered; and

   b. a compilation of data comparing key PK parameters in males and females (since Gonal-F is currently approved for a female indication only).

If you have any questions, please contact Eufrecina DeGuia, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
(DRUDP; HFD-580)
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-378/S-006

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

JUL 30 1999

Attention: Thomas A. Lang
Sr. Vice President, Regulatory Affairs

Dear Mr. Lang:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Gonal-F

NDA Number: 20-378

Supplement Number: S-006

Date of Supplement: July 26, 1999

Date of Receipt: July 27, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on September 25, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation III
Attention: Document Control Room 17B-20
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

/S/

Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Serono
PART OF THE ARES
SERONO GROUP

MEMORANDUM -

To: Freshnie DeGuia

From: Debbie DeMuria, Pharm.D.

Cc: May 22, 2000

Subj: Gonal-F® Package Insert Revision: NDA 20-378/S-006

Dear Freshnie,

As requested for the Document Room, enclosed please find a hard copy of the FINAL Gonal-F® Package Insert (dated May 22, 2000) with the following requested changes:

- Table 11: Addition of the following statement to clarify "n": "Number of Men Achieving Sperm Concentration"
- Line 209: "Ancestry" changed to "ancestry'

I have also e-mailed a "Desk Copy" to you. All changes to the approved label are highlighted in blue.

Sincerely,

Debbie DeMuria

Debbie DeMuria, Pharm.D.
Regulatory Affairs, Serono Laboratories Inc.
(781) 681 - 2267

ORIGINAL

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MEMORANDUM -

NDA SUPP AMEND
SE1-006-BL

To: Freshnie DeGuia

From: Debbie DeMuria, Pharm.D.

Cc: May 18, 2000

Subj: Gonal-F® Package Insert Revision: NDA 20-378/S-006

Dear Freshnie,

As requested for the Document Room, enclosed please find a hard copy of the Gonal-F® Package Insert (dated May 18, 2000) with the following requested changes:

- New table 12 with pregnancy information.
- Inclusion of race in male patient demographics.
- Some male demographic data displayed as mean (range), rather than mean ± SD, as requested.
- USP units changes to USP Units throughout the document.

I have also sent a Desk Copy to your attention. All changes to the approved label are highlighted in blue; recent changes in this version are highlighted in red and underlined.

Sincerely,

Debbie DeMuria

Debbie DeMuria, Pharm.D.
Regulatory Affairs, Serono Laboratories Inc.
(781) 681 - 2267

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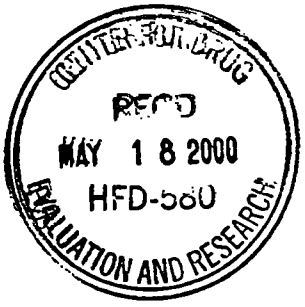
FAX (781) 871-6754

May 17, 2000

Susan Allen, M.D.
Acting Director
Division of Reproductive and Urologic Drug
Products, HFD-580 (Room 17-B-45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DUPLICATE



NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Response to Information Request NEW CORRESP

Dear Dr. Allen:

SNC-006

Reference is made to NDA 20-378 for Gonal-F® (follitropin alfa for injection) approved on September 29, 1997. Reference is also made to our supplemental New Drug Application (S-006) dated July 26, 1999, which provides for revised labeling to include a new indication; namely, administration of Gonal-F® with concommitant chorionic gonadotropin for the stimulation of spermatogenesis in men who have primary or secondary hypogonadotropic hypogonadism.

Further reference is made to a request from the Division on May 10, 2000 for patent information relevant to this supplemental application. Accordingly, this letter provides confirmation that Serono currently has no patent related to the use of Gonal-F® in males for this indication.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of Code of Federal Regulations.

Should you have any concerns about this submission, please contact me at (781)-681-2298 or Debbie DeMuria, Pharm.D., Sr. Regulatory Affairs Associate at (781) 681-2267.

Sincerely,

Pamela Williamson-Joyce
Vice President, Regulatory Affairs

cc: Eufrecina DeGuia: Desk Copy

FAX

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Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

Date: 16 May 2000

9

To: Ms. Freshnie DeGuia
(HFD-580)

re: Gonal-F NDA 20-378 (S-006)
Phone: (301) 827-4260
Fax phone: (301) 827-4267
CC:

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: (781) 681 - 2287
Fax phone: (781) 878 - 5001

REMARKS: ☐ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

Please find enclosed the additional information as requested on the 9 patients enrolled in Clinical Study 6793 after the March 11, 1998 cutoff, as discussed with Dr. Benson in our telecon this afternoon:

- **Primary Efficacy Information:**(Sperm concentration) as well as sperm count, motility and morphology in 9 patients.
- **Safety:** Updated safety information from Serono's database as of today (May 16, 2000) for the requested 9 patients. (Note: There were no AE's recorded for patient 040004).

Note that the post cut-off data is in the process of being reviewed for data-queries and can not be considered fully validated at this point.

Please call if you have any questions.

Sincerely,

debbie

debbie

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Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

Date **16 May 2000**

13

To: **Ms. Freshnie DeGuia**
(HFD-580)

re: **Gonal-F NDA 20-378 (S-006)**
Phone (301) 827-4260
Fax phone: (301) 827-4267
CC:

From: Debbie DeMurla, Pharm.D.
Regulatory Affairs

Phone: **(781) 681 - 2267**
Fax phone: **(781) 878 - 5001**

REMARKS: ☒ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

The Annual Report for Gonal-F® Male IND # 43,865 follows (Serial No. 032, dated April 2, 2000). As of the reporting period covered in the Annual report (Nov. 1998 through Oct. 31, 1999), there were no serious AE's reported.

Please let me know if this is sufficient information for the Medical Review as we query our database for more up-to-date information

Sincerely,

debbie

debbie

Serono

PART OF THE ARES
SERONO GROUP

MEMORANDUM -

To: Freshnie DeGuia

From: Debbie DeMuria, Pharm.D.

Cc: May 15, 2000

Subj: Gonal-F® Package Insert Revision: NDA 20-378/S-006

Dear Freshnie,

As requested for the Document Room, enclosed please find a hard copy of the Gonal-F® Package Insert with the following requested change:

- Line 221: the period after the word, "couples" has been removed.
- Lines 501, 505 & 509: For consistency and clarity the units on Profasi® have been changed from "U" to "USP units" as in lines 461 and 471.

I have also sent Desk Copies to your attention for Dr. Mann and Dr. Allen, as requested. All changes to the existing label are highlighted in blue.

Sincerely,

debbie deMuria

Debbie DeMuria, Pharm.D.
Regulatory Affairs

FAX

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PART OF THE ARES SERONO GROUP

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

Date **11 May 2000**

To: **Ms. Freshnie DeGuia**
(HFD-580)

re: **Gonal-F NDA 20-378 (S-006)**
Phone: (301) 827-4260
Fax phone (301) 827-4267
CC:

From: Debbie DeMuria, Pharm.D.
Regulatory Affairs

Phone: **(781) 681 - 2267**
Fax phone: **(781) 878 - 5001**

REMARKS: ☒ Urgent ☒ For your review ☐ Reply ASAP ☐ Please comment

Dear Freshnie,

Revised Gonal-F PI. Please call me with any questions.

Sincerely,

debbie

pages 1 - 23

-> pages 24 - 33

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NDA SUPP AMEND

April 20, 2000 SE1-006-BB

Susan Allen, M.D.
Acting Director
Division of Reproductive and Urologic Drug
Products, HFD-580 (Room 17-B-45)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DUPLICATE

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
SNDA Male hypogonadotropic hypogonadism
Response to Biopharm Request

Dear Dr. Allen:

Reference is made to NDA 20-378 (Gonal-F®) approved on September 29, 1997. Reference is also made to supplemental NDA (S-006) dated July 26, 1999 for a new indication of Gonal-F® in males with hypogonadotropic hypogonadism. Further reference is made to the March 27, 2000 telephone call with Dr. Chatterjee during which he requested the following information:

1. **The 3 Japanese study reports (GF 5665, GF 5826 & GF 6570) do not follow the Final 1992 Guideline (Statistical Procedures for Bioequivalence Studies using a 2-treatment Design). Please provide the output according to the FDA Guidance, specifically the point estimate ratios (confidence intervals) for the studies.**

The studies were performed in 1992-1993 according to Japanese guidelines for the main purpose of pursuing registration in Japan. As these were the only available pharmacokinetic data in male volunteers, they were submitted as part of Gonal-F® supplemental NDA S-006 for the purpose of documenting the pharmacokinetic profile and the safety of Gonal-F® in male subjects. Accordingly it was agreed with Dr. Chatterjee during an April 4 telephone conversation that it would not be necessary to provide the data per the FDA Guideline, since demonstration of bioequivalence as such is not relevant to this application.

2. In the sNDA, a radiometric assay was used to re-calculate the dose. As this is the basis for the information provided, why did we do it and how did we do it?

In the PK studies, a radio immunoassay was used to measure drug concentrations in the serum which are then expressed in IU/L. The nominal dose is expressed in IU's based on the bioassay belonging to the release tests for the drug. To avoid any confusion, the nominal dose (bioassay) was assessed by the same immunoassay that was used for measuring drug concentrations in serum and therefore expressed in the same units (immunoassay IU's). Thus, in the calculation of the pharmacokinetic parameters, this method provides a better consistency. The content of an appropriately reconstituted vial is analyzed by the same immunoassay as if a serum sample was assessed.

3. Please provide electronic formats (CD or floppy disk) of the PK studies

Electronic copies of the study reports are provided with this submission. Files of reports 5665/5826 and 6570 were scanned using Optical Character Recognition (OCR). The files are Microsoft Word files that allow the use and manipulation of the data. Please note that for the convenience of the reviewer these files were also provided by e-mail on April 7, 2000.

Studies 5665/5826

- OCR: From the start of report to references and from Appendix B to Appendix E
- Scan: From Tables to Appendix B are scanned and data can not be manipulated. However, these figures are items such as Dosing schedule and Certificates of Analysis, which can be cut and pasted as pictures.

Study 6570:

- OCR: From page 1 to page 9
- Scan: From page 10 to page 13
- OCR: From page 14 to page 17
- Scan: up to the end

4. Is there any literature (or in-house data) to support the PK gender differences (male vs. female) for Gonal-F®?

Please also refer to the data that were submitted on November 19, 1999 (Attachments VII and VIII) in response to a question we had received from Dr. Chatterjee. In that submission, we performed a statistical comparison of the Japanese studies with the Phase I studies submitted in the original Gonal-F® NDA 20-378 and recent European (IMP 20484) and Japanese phase I (IMP 20493) studies. The conclusion was:
"In conclusion, these compiled data support the fact that the pharmacokinetics of r-hFSH are not different among genders, nor between Asian and Caucasian subjects."

We hope this clarifies that adequate data is available in the current application to document the pharmacokinetic, safety and efficacy of Gonal-F® in the target population.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of 18 U.S.C. and Title 21 of Code of Federal Regulations.

Should you have any concerns about this submission, please contact me at (781) 681 2104 or Debbie DeMuria, Pharm.D., Sr. Regulatory Affairs Associate at (781) 681-2267.

Sincerely,

Dennis Bucceri
Vice President, Regulatory Affairs USA

cc: Eufrecina DeGuia (Desk Copy)

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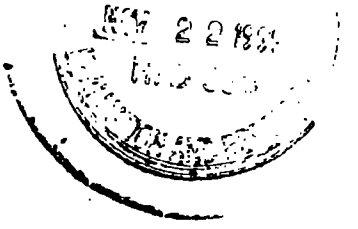
NDA SUPP AMEND
SE1-006-B?



November 19, 1999

Lisa D. Rarick, M.D.
Director, Division of Reproductive and Urologic
Drug Products HFD-580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-378 / S-006
Gonal-F® (follitropin alfa for injection)
Male hypogonadotropic hypogonadism: Response to Clinical Pharmacology and Biopharm Review

Dear Dr. Rarick,

Reference is made to NDA 20-378 for Gonal-F® (follitropin alfa for injection) approved on September 29, 1997. Reference is also made to our supplemental New Drug Application (S-006) dated July 26, 1999, which provides for revised labeling to include a new indication; namely, administration of Gonal-F® with concomitant chorionic gonadotropin for the stimulation of spermatogenesis in men who have primary or secondary hypogonadotropic hypogonadism.

Further reference is made to a September 1, 1999 teleconference between D. DeMuria, E. DeGuia, and Dr. Chatterjee (Biopharm. Reviewer) and the October 21 letter from the Division in which Serono was asked to provide Analytical Validation Reports with QC information for three PK studies submitted in the supplement (Studies GF 5665, GF 5826 and GF 6570).

A response with appropriate attachments is provided in the enclosure to this letter, as requested and in the order outlined in the October 21 letter from the Division.

Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential, proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate, or the undersigned at (781) 681-2267.

Yours sincerely,

Dennis J. Bucceri
Vice President, Regulatory Affairs

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NEW CORRESP

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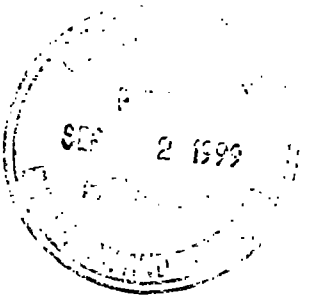
FAX (781) 871-8754

September 1, 1999

Lisa Rarick, M.D., Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA 20-378
Gonal-F® (follitropin alfa for injection)
General Correspondence:

Dear Dr. Rarick,

Reference is made to NDA 20-378 for Gonal-F® (follitropin alfa for injection) approved on September 29, 1997. Further reference is made to a supplement New Drug Application, S-006, submitted on July 26, 1999 which provided for revised labelling and clinical data to support a new indication: administration of Gonal-F® with concomitant chorionic gonadotropin for the stimulation of spermatogenesis in males with hypogonadotropic hypogonadism. Reference is also made to a telephone conversation between Ms. Eufrecinia DeGuia and D. DeMuria on August 11, 1999, whereby Serono was asked to submit in writing to the Division that the above referenced supplement does not provide a CMC change to either drug substance, drug product or drug strength as requested by Dr. Rhee.

Accordingly, this letter serves as written confirmation that Clinical Supplement S-006 provides for a labelling change only for the indication of male hypogonodotropic hypogonadism and does not provide for a change in formulation or any change to the chemistry or manufacturing of the drug substance or drug product.

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Pharm.D., Senior Regulatory Associate at 781-681-2267.

Yours sincerely,

Thomas A. Lang,
Senior Vice President, Regulatory Affairs

cc: Ms. E DeGuia, FDA (by fax)

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August 30, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
SEP - 1 1999
HFD-580

NSM 9.13.99

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Noted for 11/15/99

11/13/99

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Correspondence: Response to FDA's Questions

Dear Dr. Rarick:

Reference is made to our approved New Drug Application, NDA 20-378, for Gonal-F® and the supplemental New Drug Application (S-006) for a new indication in male hypogonadotropic hypogonadism submitted July 26, 1999. Reference is also made to a request for additional information from Dr. Marks conveyed to Serono by Ms. Eufrecinia DeGuia on August 23, 1999.

Dr. Marks requested the following information:

1. A listing of any meetings, such as End of Phase-II, pre-NDA or general correspondence with the Division, specifically whether the design of the studies had been discussed.

2. Dr. Marks questioned whether the selection of 1.5 x 10^6 sperm/mL was low relative to achieving efficacy and requested all information available about pregnancy outcomes of partners of males treated with Gonal-F® (i.e., number of pregnancies, outcomes, etc.)

1. Serono's responses to the above inquiry regarding communication with the FDA relative to this sNDA are as follows:

- On two occasions, Serono submitted to the Division of Metabolism and Endocrine Drug Products our intention to conduct clinical trials with Gonal-F® in males for the treatment of hypogonadotropic hypogonadism. Each submission included the design and protocol of the intended studies.

- In a letter dated August 18, 1993 submitted to IND 38,712 (Serial No. 019), Serono notified the Agency of its intent to submit a marketing application to indicate Gonal-F® for the treatment of

male hypogonadotropic hypogonadism based on a phase III non-comparative clinical study conducted in Europe. A copy of the clinical study protocol (GF 5844) was attached. The scientific rationale for the use of Gonal-F® in the proposed indication including reason for our study design was described in the coverletter (See Attachment 1). The purpose of the submission was to obtain FDA's comments on the adequacy of the scientific and regulatory basis for filing a marketing application with a single study. Our records indicate a telephone contact with the Endocrine Division on October 4, 1993 to follow-up on the aforementioned proposal. No comments were received from FDA.

- Serono initiated a second study (Study 6793) to gain experience in US patients in a phase III non-comparative study to evaluate the safety and efficacy of Gonal-F® for the treatment of male hypogonadotropic hypogonadism. This submission was made in a letter dated June 29, 1994 to IND 43,865 (Serial No. 006). Again, no comments from the Agency were received by Serono and the US Clinical Program for the treatment of male hypogonadotropic hypogonadism began.

- Serono informed FDA of its intention to file an sNDA for Gonal-F® in a telephone contact between D. DeMuria and D. Moore on March 10, 1999. There was no End of Phase-II or pre-NDA meeting between the Division and Serono before the submission of the referenced sNDA.

2. Serono's response to Dr. Marks' questions regarding clinical endpoints and outcomes is as follows.

- Relative to Dr. Marks' question regarding our selection of a minimum sperm density of $\geq 1.5 \times 10^6$/mL as the primary efficacy variable, the choice of that endpoint for adult male patients with hypogonadal hypogonadism (HH) was based on medical literature (Burris, et al; see reference as Attachment 3) and clinical experience (Whitcomb, et al; see reference as Attachment 4). In the study by Burris et al, 22 of 24 adult men with HH (92%) achieved 40 pregnancies in their partners during gonadotropin therapy. Semen analyses were available for 31 of those pregnancies and 16% of patients achieving a pregnancy had a sperm count less than 1.0×10^6/mL. Similarly, Whitcomb demonstrated that GnRH replacement therapy in male HH patients results in normal fertility with quantitatively low but qualitatively normal semen parameters. Therefore, it has been established that there is a low threshold for achievement of fertility in the male HH patient population in the absence of an intrinsic testicular defect.

  The choice of a 1.5×10^6 sperm/mL endpoint is further discussed in Section 1.2.4 of the Summary of the sNDA (volume 1) and in Sections 5.2.2, 5.2.2, and 7.3 of the individual study reports for Studies 5844, 6410, and 6793, respectively.

- Regarding pregnancy rates, the attainment of pregnancy in a partner desiring pregnancy is an important supportive validation of the efficacy of Gonal-F® for the treatment of male HH. In this indication, not all patients necessarily have a reproductive partner or immediately desire pregnancy. Men with hypogonadotropic hypogonadism may be profoundly delayed in their psychosexual development and the consideration of fertility may not be their immediate focus of treatment. In addition, the timely attainment of pregnancy may be complicated by additional female reproductive

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factors. Therefore, attainment of pregnancy was appropriately assessed as an important but secondary efficacy endpoint in all three studies.

Table 1, below, (Table 19 in Section 6.2.4.4, page 70 of the Clinical Summary of the sNDA) provides a summary of pregnancy information in partners of patients in all three Gonal-F® male HH studies combined (5844, 6410, and 6793). More detailed pregnancy information from partners of males treated with Gonal-F® enrolled in the 3 clinical studies is provided in Attachment 2.

Table 1. Secondary Efficacy Endpoints: Pregnancies in Partners, by Study (Patient Population: All Patients in All 3 Studies, Combined)

	Study 5844	Study 6410	Study 6793
Number of Patients Enrolled	32	10	30
Number of Patients Seeking Fertility	7	10	24[b]
Pregnancies Achieved [c]	6[a]	3	3
Outcomes:			
Healthy Baby	5	2	1
Miscarriage	1	1	1
Preclinical Spontaneous Abortion	0	0	1
Section(s) of Study Report	10.5 2 7	10.5 2 7	11 4 2 2.13

(a) These six pregnancies occurred in four partners.

(b) At the time of the data cutoff for the interim analysis for Study 6793, 13 patients had either completed the scheduled 18 months of Gonal-F treatment or had been withdrawn from the study after reaching a defined discontinuation endpoint per the study protocol. Just 8 of those 13 patients had a current partner who desired pregnancy.

(c) The pregnancy rates for completed patients in all three studies were 57.1% (4 of 7 patients), 30.0% (3 of 10 patients), and 37.5% (3 of 8 patients) for studies 5844, 6410, and 6793, respectively.

It should be noted that pregnancies were only reported while a patient was enrolled in each study or shortly thereafter.

Of the 72 patients enrolled in Studies 5844, 6410 and 6793, 41 (56.9%) had stated their interest in achieving a pregnancy and all but 4, in Study 6793, had a current partner. Among the 37 patients seeking fertility who had partners, 12 pregnancies occurred in 10 partners.

The outcome of these 12 pregnancies were: 8 healthy babies born, 3 miscarriages, and 1 biochemical pregnancy. The pregnancy rates for completed patients in all three studies were 57.1% (4 of 7 patients), 30.0% (3 of 10 patients), and 37.5% (3 of 8 patients) for Studies 5844, 6410, and 6793, respectively.

Overall, the rate of achievement of pregnancy in the limited period of exposure allowed by the individual studies can be considered quite satisfactory for this patient population.

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Please note that Serono Laboratories, Inc. considers this submission and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any questions concerning this submission, please contact Debbie DeMuria, Pharm.D., Sr. Regulatory Associate at (781) 681-2267, or the undersigned.

Sincerely,

Rosann Leonard for
Thomas A. Lang,
Senior Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

cc: Ms. E. DeGuia (FDA) by fax

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ORIGINAL

NDA NO. 20378 REF. NO. SE1-006

NDA SUPPL FOR efficacy

Confidential

Serono
PART OF THE ARES-SERONO GROUP
SERONO LABORATORIES, INC
100 LONGWATER CIRCLE
NORWELL, MA 02061 / USA
(800) 283-8088
TEL (781) 982-9000
FAX (781) 871-6754

July 26, 1999

Lisa Rarick, M.D., Director,
Division of Reproductive and Urology
Drug Products, HFD 580
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 27 1999
HFD-580

NDA 20-378
Gonal-F (follitropin alfa for injection)
Supplement for Male hypogonadotropic hypogonadism

Dear Dr. Rarick,

Reference is made to IND 43,865 and IND 38,712 for Gonal-F (follitropin alfa for injection) submitted on November 5, 1993 and January 24, 1992, respectively. Reference is also made to NDA 20-378 for Gonal-F (follitropin alfa for injection) approved on September 29, 1997. Reference is also made to Orphan Drug Application 98-1193, which was approved by the agency on December 21, 1998 for the indication being sought in the supplemental New Drug Application (sNDA).

In accordance with the Title 21 CFR 314.70(b)(3) we herewith submit in duplicate a supplement to our approved New Drug Application, NDA 20-378, for Gonal-F (follitropin alfa for injection). The supplement provides for revised labeling to include a new indication; namely, administration of Gonal-F with concomitant chorionic gonadotropin for the stimulation of spermatogenesis in men who have primary or secondary hypogonadotropic hypogonadism.

Male hypogonadotropic hypogonadism is a rare disorder of the reproductive function. The indication has been granted orphan status by the agency. The data on which we rely for support of the new indication are derived from three Phase III, controlled, non-comparative clinical studies to assess efficacy and safety (Study 5844-Europe, Study 6793-US and Study 6410-Australia). Protocols and rationale for designs for the European and American studies were submitted on August 18, 1993 (IND 38,712) and June 29, 1994 (IND 43,865), respectively.

The results of the three studies are remarkably consistent, compelling and reproducible. Given the rarity and nature of this disorder, Serono believes that the three Phase III, controlled, non-comparative studies are adequate in design and provide substantial evidence of the safety and efficacy of Gonal-F in the male indication.

In addition to the clinical data mentioned above, the sNDA includes the results of single and multiple dose human pharmacokinetic studies conducted in male volunteers. Also included are two long-term toxicology study reports—52 weeks in male rats and monkeys. The full reports of these toxicology studies were submitted to IND 38,712 on October 22, 1993. The sNDA consists of 44 (forty four) volumes. The breakdown of these volumes is as follows:

Volume 1:	Cover letter, FDA Forms 356h and 3397, Orphan Drug Designation, Overall Table of Content, Debarment Statement, sNDA Summary and the draft revised package insert.
Volumes 2-44:	Technical Sections
• Volume 2-6:	Section 5 – Preclinical Pharmacology and Toxicology Reports
• Volume 7-10:	Section 6 – Human Pharmacokinetics Reports
• Volume 11-29:	Section 8 – Clinical Study Reports
• Volume 30-44:	Section 10 – Statistical Methodology

For convenience of the reviewers, copies of the sNDA summary which contains the Integrated Summary of Safety and Efficacy are also provided at the beginning of each Technical Section. Please note that there is no change to the approved Chemistry, Manufacturing, and Controls of the drug product. drug substance & strength

Please note that Serono Laboratories, Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

Should you have any concerns about this submission, please contact Debbie DeMuria, Regulatory Affairs Associate, or the undersigned at 781-982-9000.

Yours sincerely,

Thomas A. Lang
Senior Vice President
Regulatory Affairs

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

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

DOCUMENT CONTROL COPY

December 21, 1998

Serono Laboratories, Inc.
100 Longwater Circle
Norwell, MA 02061

Attention: Thomas Lang
Senior VP, Regulatory Affairs and Quality Assurance

Dear Mr. Lang:

Reference is made to the orphan product application of October 23, 1998, submitted pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (FFDCA) for the designation of Gonal-F (follitropin alfa, recombinant) as an orphan product (application #98-1193).

We have completed the review of this application and have determined that Gonal-F qualifies for orphan designation for the initiation and re-initiation of spermatogenesis in adult males with reproductive failure due to hypothalamic or pituitary dysfunction, hypogonadotropic hypogonadism.

Please be advised that if Gonal-F were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of Gonal-F as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Michael W. Dreis, PharmD, MPH at (301) 827-0990.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan product designation.

Sincerely yours,

/S/

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

Teleconference Minutes

Date: May 18, 2000 **Time:** 9:30-10:00 AM **Location:** PKLN; Rm 17B45

NDA 20-378/S-006 **Drug Name:** Gonal-F® (follitropin alfa for injection)

Indication: male hypogonadotropic hypogonadism

Sponsor: Serono Laboratories

Type of Meeting: Guidance (labeling)

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendee:
Eufrecina DeGuia, Regulatory Project Manager, DRUDP (HFD-580)

External Participant:
Debbie DeMuria – Senior Regulatory Affairs Associate

Meeting Objectives: To convey to the sponsor the minor changes that need to be made on the revised label submitted on May 15, 2000.

Background: Labeling negotiations are on-going for this efficacy supplement and the action goal date is May 27, 2000.

Decision Points:

- the following recommended changes were conveyed to the sponsor:
  - on page 14, line 198, Standard Deviation (SD) is omitted; delete "$\pm$ 7.7" and replace with "(range 16 to 48)"
  - on page 14, line 200, add the sentence " Thirty one patients of the patients were Caucasian and one was Asian."
  - on page 14, line 201, add the phrase "mean age was 36 (range 26 to 48) years" after "In Study 6410.. and delete "patients were 36 $\pm$ 7 years old"
  - on page 14, line 203-204, add the sentence "Seven patients were Caucasian and three were Asian." after the word anosmic
  - on page 14, line 205, delete "+ 5.0 years, add "(range 22 to 44 years)" after 30.1
  - on page 14, line 209, add the sentence "Twenty five of the patients were Caucasian, three were Asian, and one each of Moroccan and Indian ancestry.
  - on page 15, below Table 11, insert Table 12 entitled "Pregnancy Outcome in [redacted]
  - on page 15, line 218, in the sentence that starts with "Thus..." delete "fertility" and replace with "pregnancy (clinical and chemical)"
  - on page 15, line 219, insert [redacted] 'partners" and "seeking"
  - on page 16, line 241, delete "and" after the word hypogonadism

- on page 16, under **Selection of Patients,** add the sentence "Prior to Gonal-F therapy for azoospermia in patients with hypogonadotropic hypogonadism, serum testosterone levels should be normalized." as statement # 3.
- table 12 and 13 should be renumbered as Table 13 and 14
- the "u" in units in all areas of the label where the dose of hCG is mentioned should be capitalized
- on page 28, line 427, the word "mild" should be deleted
- on page 28, line 432, spelling of "patients" should be corrected
- on page 31, line 501, "(1,000 USP units three times a week)" should be deleted and replace with "(1000 to 2,250 USP Units two to three times per week
- on page 31, line 504-506, the sentence that states " Most patients..." should be deleted.

Action Items:

- the sponsor will send the revised label today, May 18, 2000 via email (followed by hard copy to the Division Document Room)

/S/

Signature, Recorder and Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Teleconference Minutes

Date: May 16, 2000 **Time:** 3:15 - 3:30 PM **Location:** PKLN; Rm 17B45

NDA 20-378/S-006 **Drug Name:** Gonal-F® (follitropin alfa for injection)

Indication: male hypogonadotropic hypogonadism

Sponsor: Serono Laboratories

Type of Meeting: Guidance (labeling)

Meeting Chair: Dr. George Benson **External Participant Lead:** Dr. Louie O'Dea

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
George Benson, M.D. – Medical Officer, Division of Reporductive and Urologic Drug Products; HFD-580
Eufrecina DeGuia, Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Debbie DeMuria – Senior Regulatory Affairs Associate
Louis O'Dea, M.D. – Vice President, Clinical Development, Reproductive and Women's Health
George Hemsey – Medical Research Associate

Meeting Objectives: To clarify with the sponsor whether they have data on the nine patients remaining on Gonal-F treatment after the data cutoff and to request a safety update for this application.

Background: Labeling negotiations are on-going for this efficacy supplement and the action goal date is May 27, 2000.

Decision Points:
- as of March 1998 cut-off date (on Study Report 6793), nine patients were still enrolled in the study; the sponsor was asked to submit safety update data on those nine patients, most especially on the seven patients that finished treatment; the sponsor noted that two patients remain on treatment until October 2000
- the Division requested the safety update data for the following patients:
  - 020004
  - 030004
  - 030005
  - 030006
  - 030007
  - 030008
  - 030009
  - 040004
  - 070003

Action Items:

- the sponsor will send the primary efficacy and safety data for all nine patients today, May 16, 2000

/S/
Signature, Recorder

/S/
Concurrence, Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Teleconference Minutes

Date: May 15, 2000 **Time:** 10:45-10:55 AM **Location:** PKLN; Rm 17B45

NDA 20-378/S-006 **Drug Name:** Gonal-F® (follitropin alfa for injection)

Indication: male hypogonadotropic hypogonadism

Sponsor: Serono Laboratories

Type of Meeting: Guidance (labeling)

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendee:
Eufrecina DeGuia, Regulatory Project Manager, DRUDP (HFD-580)

External Participant:
Debbie DeMuria – Senior Regulatory Affairs Associate

Meeting Objectives: To convey to the sponsor the minor changes that need to be made on the revised label submitted on May 11, 2000.

Background: Labeling negotiations are on-going for this efficacy supplement and the action goal date is May 27, 2000.

Decision Points:
- the following recommended changes were conveyed to the sponsor:
  - in line 221, the period after couples should be deleted
  - in lines 501, 505 (in two places) and 509, the hCG units are referred to as "U" while on lines 462 and 471, the hCG units are referred to as "USP units"; for consistency and clarity, all of the units should be referred to as "USP Units"; therefore, this change should be made in lines, 501, 505 (in two places) and 509

Action Items:
- the sponsor will send the revised label via email (followed by hard copy to the Division Document Room)

/S/

Signature, Recorder and Chair

NOTE: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcome.

Meeting Minutes

Date: April 26, 2000 **Time:** 11:00-11:45 am **Location:** Parklawn; 17B-45

NDA 20-378/S-006 **Drug:** Gonal-F (follitropin alfa for injection)

Indication: male hypogonadotropic hypogonadism

Sponsor: Serono Laboratories, Inc.

Type of Meeting: 9-month Status and Labeling Meeting

Meeting Chair: Mark Hirsch, M.D.

Meeting Recorder: Jeanine Best (for Eufrecina DeGuia)

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Mark Hirsch, M.D., Medical Officer, DRUDP (HFD-580)
George Benson, M.D., Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
DJ Chatterjee, Ph.D., Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics, (OCPB) @ DRUDP (HFD-580)
Terri Rumble, B.S.N, Chief, Project Management Staff, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the current review status and labeling issues of the application.

Discussion:
Chemistry:
- Gonal-F is an approved drug; sponsor is seeking approval for a new indication; no chemistry review required
- Label review will be done and revised if necessary
- Profasi (hCG) is listed with either International Units (IU), or Units U.S.P. following the dose throughout the NDA and the label; PDR lists Units U.S.P.; DRUDP must clarify correct use with the sponsor and the equivalence of the units since both are being used interchangeably in the NDA; the label will be revised for consistency

Clinical Pharmacology:
- review completion pending on sponsor's response to our request for a "male" Clinical Pharmacology sections in the label
- "N" Drive label revisions to include comment ("please insert male section here")

Clinical:

- review is complete; acting team leader concurrence should be complete by 5/1/00 (done 04.28.00)
- awaiting requested pathology report on one mastectomy patient (received 04.27.00)
- label revisions will be completed on "N" Drive by COB today
  - titles of Tables 10 and 11 were expanded to reflect study results
  - in **INDICATIONS and USAGE** section, under the title "Selection of Patients", azoospermia was added for clarification
  - in **DOSING and ADMINISTRATION** section, administration of drug product was clarified

Decisions made:

- anticipating support for an Approval Action

Action Items:

- E. DeGuia to forward label revisions to sponsor by 5/1/00 (label was sent 05.02.00)

/S/ /S/

Minutes Preparer **Concurrence, Chair**

cc:
Original IND
HFD-580/DivFile
HFD-580/PM/DeGuia,JBest
HFD-580/Mann/Hirsch/Benson/Rhee/Chatterjee/Rumble

drafted: JAB/April 26, 2000
concurrence: TRumble05.02.00/GBenson,MHirsch,MMann,DChatterjee05.08.00
final:EDeGuia05.10.00

MEETING MINUTES

DeGuia

Meeting Minutes

Date: March 27, 2000 **Time:** 11:30 AM – 12:15 PM **Location:** Parklawn; 17B-43

NDA 20-378/S-006 **Drug:** Gonal-F (follitropin alfa for injection)

Indication: male hypogonadotropic hypogonadism

Sponsor: Serono Laboratories

Type of Meeting: 8-month Status Meeting

Meeting Chair: Daniel Shames, M.D.

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Daniel Shames, M.D. – Urology Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Terri Rumble, B.S.N. – Chief, Project Management Staff, DRUDP (HFD-580)
Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics Review (OCPB) @ DRUDP (HFD-580)
Karen Davis-Bruno, Ph.D. - Pharmacologist, DRUDP (HFD-580)

Meeting Objective: To discuss the status of this application.

Discussion:
Clinical
- review of two studies are complete; third study under review
- label appears to be straightforward; trial should be described in the Clinical Section; changes in the label will be made through electronic revisions on the N drive

Biopharmaceutics
- review is pending
- confidence interval (CI) of point estimate ratio should be requested from the sponsor; CI of the mean should be 80-125%
- regarding radiometric assay, the sponsor should clarify why corrections are being made and how the calculations are being performed
- request electronic copies of all PK study reports and published PK literature (for male and female)

Pharmacology and Toxicology
- review is finished, pending Team Leader sign off

Statistics
- No review required (see Filing Meeting dated September 1, 1999)

Chemistry
- No review required (see Filing Meeting dated September 1, 1999)

Action Items:
- Request electronic copies of all PK study reports and published PK literature (for male and female)
- next status/labeling meeting will be held on April 26, 2000.

/S/
Minutes Preparer

/S/
Concurrence, Chair

cc:
Original IND
HFD-580/DivFile
HFD-580/Rumble/EDeGuia
HFD-580/DShames/AParekh/DChatterjee/KDavis-Bruno/GBenson

drafted: April 14, 2000
concurrence: DMoore04.20.00/KDavis-Bruno,DChatterjee04.20.00/DShames05.01.00
final: EDeGuia05.02.00

MEETING MINUTES

MEETING MINUTES

Date: September 1, 1999 **Time:** 10:30 – 11:30AM **Location:** Parklawn, 17B43

NDA: 20-378/006 **Drug Name:** Gonal-F® (follitropin alfa for injection)

Indication: Male Hypogonadotropic Hypogonadism

Type of Meeting: Filing Meeting

Meeting Chair: Dr. Lisa Rarick

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Lisa Rarick, M.D., Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Daniel Shames, M.D., Team Leader, DRUDP (HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP (HFD-580)
Terri Rumble, Chief, Regulatory Project Management Staff, DRUDP (HFD-580)
Eufrecina De Guia, Regulatory Project Manager, DRUDP (HFD-580)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Dhruba Chatterjee, Ph.D. – Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Kate Meaker, M.S. - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Lana L. Pauls, M.P.H. -Associate Director, DRUDP (HFD-580)

Meeting Objectives: To discuss and determine the fileability of this efficacy supplement.

Background: Gonal-F was approved in September 29, 1997 for ovulation induction and pregnancy. This supplement is for a new indication, Male Hypogonadotropic Hypogonadism, which received an Orphan Drug designation in December 1998. This application will require a Standard Review and the Goal Dates are May 27, 2000 (for the 10-month review clock) or July 27, 2000 (for the 12-month review clock).

Decisions reached:

Clinical:
- from a clinical perspective, the application is fileable
- the new indication is derived from three small Phase 3, controlled, non-comparative studies; study designs varied across trials, doses and dosing intervals
- primary endpoint was achievement of sperm density >1.5 million/mL at any point during 18 months of combined treatment and pregnancy data/outcome as secondary endpoint
- safety data presented is consistent with guidelines based on world-wide knowledge regarding this drug
- the Division may require the sponsor to submit a Phase 4 commitment for a dose justification study

Chemistry:

- no review required; there are no CMC changes to either drug substance, drug product or drug strength from the Gonal-F application approved in September 1997; the sponsor submitted this confirmation of no change in writing on September 1, 1999

Clinical Pharmacology and Biopharmaceutics

- this application is fileable
- the sponsor will be required to submit PK information on different ethnic groups

Statistics:

- no review required; there are no comparisons, tests, or other statistical methods applied for the three efficacy studies; GF 5844, GF 6410 and GF 6793

Pharmacology/ Toxicology

- the application is fileable

Action Items:

- request the sponsor to send PK analytical validation reports with QC information on the studies in Japan on Protocol Nos. 5665, 5826, 6570

/S/ _____
Signature, minutes preparer

/S/
Concurrence, Chair

drafted: ed/09.23.99

cc:
NDA Arch:
HFD-580/EDeGuia
HFD-580/LRarick/LPauls/NMarks/DShames/KMeaker/AParekh/TRumble/KRaheja/DChatterjee
Concurrences:
TRumble09.24.99/KMeaker,KRaheja,DChatterjee,DShames09.28.99/LRarick09.29.99/NMarks10.4.99

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Serono Laboratories, Inc.

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Serono Laboratories, Inc.

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 20-378/S-006
Gonal-F® (follitropin alfa for injection)
Serono Laboratories, Inc.

Advertising Material

No advertising material has been submitted.