

Follistim®

(follitropin beta for injection)

FOR SUBCUTANEOUS OR INTRAMUSCULAR USE ONLY

DESCRIPTION

Follistim® (follitropin beta for injection) contains human follicle-stimulating hormone (hFSH), a glycoprotein hormone which is manufactured by recombinant DNA (rDNA) technology. Follitropin beta has a dimeric structure containing two glycoprotein subunits (alpha and beta). Both the 92 amino acid alpha-chain and the 111 amino acid beta-chain have complex heterogeneous structures arising from two N-linked oligosaccharide chains. Follitropin beta is synthesized in a Chinese hamster ovary (CHO) cell line that has been transfected with a plasmid containing the two subunit DNA sequences encoding for hFSH. The purification process results in a highly purified preparation with a consistent hFSH isoform profile and high specific activity¹. The biological activity is determined by measuring the increase in ovary weight in female rats. The intrinsic luteinizing hormone (LH) activity in follitropin beta is less than 1 IU per 40,000 IU FSH. The compound is considered to contain no LH activity.

The amino acid sequence and tertiary structure of the product are indistinguishable from that of human follicle-stimulating hormone (hFSH) of urinary source. Also, based on available data derived from physio-chemical tests and bioassay, follitropin beta and follitropin alfa, another recombinant follicle-stimulating hormone product, are indistinguishable.

Follistim® is presented as a sterile, freeze-dried cake, intended for SUBCUTANEOUS (SC) (in men and women) or INTRAMUSCULAR (IM) (women only) administration after reconstitution with Sterile Water for Injection, USP. Each vial of Follistim® contains 75 IU of FSH activity plus 25.0 mg sucrose, NF; 7.35 mg sodium citrate dihydrate, USP; 0.10 mg

polysorbate 20, NF, and hydrochloric acid, NF and/or sodium hydroxide, NF to adjust the pH in a sterile, lyophilized form. The pH of the reconstituted preparation is approximately 7.0. The recombinant protein in Follistim® has been standardized for FSH *in vivo* bioactivity in terms of the First International Reference Preparation for human menopausal gonadotropins (code 70/45), issued by the World Health Organization Expert Committee on Biological Standardization (1982). Under current storage conditions, Follistim® may contain up to 20% of oxidized follitropin beta.

In clinical trials with Follistim®, serum antibodies to FSH or anti-CHO cell derived proteins were not detected in any of the treated patients after exposure to Follistim® for up to three cycles.

Therapeutic Class: Infertility.

¹ As determined by the Ph. Eur. test for FSH *in vivo* bioactivity and on the basis of the molar extinction coefficient at 277 nm ($\epsilon_s: \text{mg}^{-1} \text{cm}^{-1}$) = 1.066.

CLINICAL PHARMACOLOGY

Follistim® (follitropin beta for injection) stimulates ovarian follicular growth in women who do not have primary ovarian failure. FSH, the active component of Follistim®, is required for normal follicular growth, maturation, and gonadal steroid production. In the female, the level of FSH is critical for the onset and duration of follicular development, and consequently for the timing and number of follicles reaching maturity. In order to effect the final phase of follicle maturation, resumption of meiosis and rupture of the follicle in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) must be given following the administration of Follistim® when patient monitoring indicates that appropriate follicular development parameters have been reached.

Follistim® when administered with hCG stimulates spermatogenesis in men with hypogonadotropic hypogonadism. FSH, the active component of Follistim® is the pituitary hormone responsible for spermatogenesis.

Pharmacokinetics

Absorption

Women

The bioavailability of Follistim® following SC and IM administration was investigated in healthy, pituitary-suppressed, female subjects given a single 300 IU dose. After SC or IM injection the apparent dose absorbed was 77.8% and 76.4%, respectively.

The SC (455.6 ± 141.4 IU*h/L) and IM (445.7 ± 135.7 IU*h/L) routes of administration were equivalent with respect to area under the curve (AUC) in healthy, pituitary-suppressed, female subjects given a single 300 IU dose. However, equivalence could not be established for C_{max} between the SC (5.41 ± 0.72 IU/L) and IM (6.86 ± 2.90 IU/L) routes of

administration.

A multiple, dose proportionality, pharmacokinetic study of Follistim® was completed in healthy, pituitary-suppressed, female subjects given IM doses of 75 IU, 150 IU or 225 IU for 7 days. Steady-state blood concentrations of FSH were reached with all doses after 4 days of treatment based on the minimum concentrations of FSH just prior to dosing (C_{\min}). Peak blood concentrations with the 75 IU, 150 IU, and 225 IU dose were 4.65 ± 1.49 IU/L, 9.46 ± 2.57 IU/L and 11.30 ± 1.77 IU/L, respectively.

A multiple, dose proportionality, pharmacokinetic study of Follistim® was completed in healthy, pituitary-suppressed, female subjects given SC doses of 75 IU, 150 IU, or 225 IU for 7 days. Steady-state blood concentrations of FSH were reached with all doses after 5 days of treatment based on the minimum concentrations of FSH just prior to dosing (C_{\min}). Peak blood concentrations with the 75 IU, 150 IU, and 225 IU dose were 4.30 ± 0.60 IU/L, 8.51 ± 1.16 IU/L and 13.92 ± 1.81 IU/L, respectively.

Men

Serum levels of FSH were measured in a clinical study that compared the effects of two different dosing schedules of Follistim® (150 IU three times a week or 225 IU twice a week) administered by SC injection concurrently with Pregnyl® (Chorionic gonadotropin for injection, USP) for induction of spermatogenesis in hypogonadotropic hypogonadal men. Serum trough concentrations of FSH measured prior to the first Follistim® injection on the Mondays of active treatment period (weeks 17 to 64) and one week after the end of treatment period are presented in Figure 1.

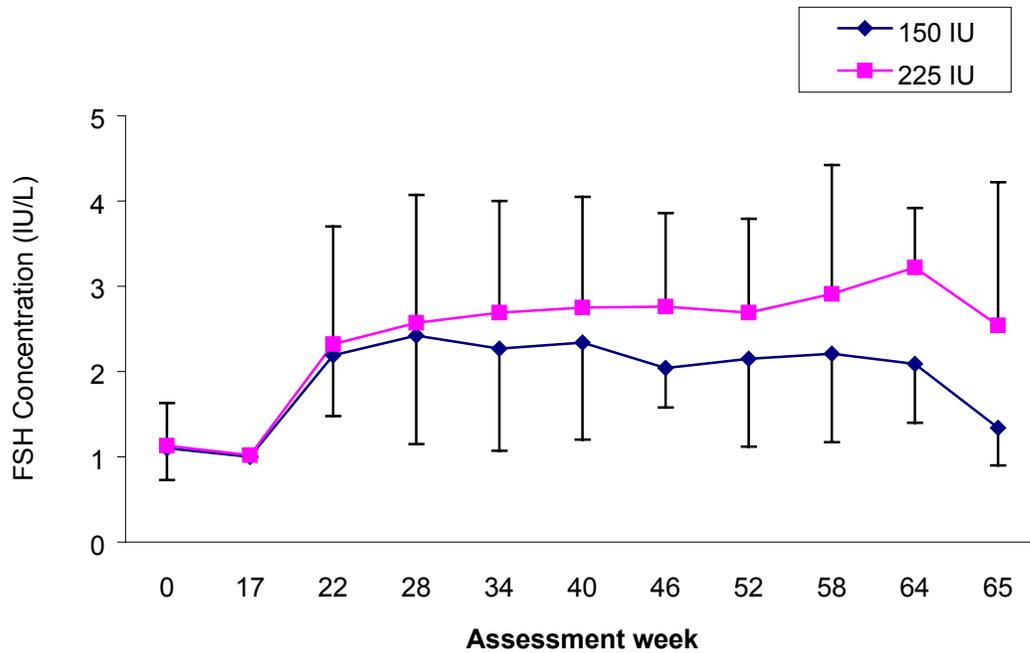


Figure 1. Mean (SD) serum trough concentrations of FSH in men following SC administration of Follistim[®] in two different dosing schedules (150 IU three times weekly or 225 IU twice weekly). Administration of FSH was started at week 17.

Mean serum trough concentrations of FSH remained fairly constant over the treatment period. At the end of treatment (week 64), the mean serum trough concentrations of FSH were 2.09 IU/L in the 150 IU group and 3.22 IU/L in the 225 IU group.

Distribution

The volume of distribution of Follistim[®] in healthy, pituitary-suppressed, female subjects

following intravenous administration of a 300 IU dose was approximately 8 L.

Metabolism

The recombinant FSH in Follistim® is biochemically very similar to urinary FSH and it is therefore anticipated that it is metabolized in the same manner.

Elimination

The elimination half-life following a single IM dose (300 IU) of Follistim® in female subjects was 43.9 ± 14.1 hours (mean \pm SD). The elimination half-life following a 7-day IM treatment with 75 IU, 150 IU or 225 IU was 26.9 ± 7.8 hours (mean \pm SD), 30.1 ± 6.2 and 28.9 ± 6.5 , respectively.

Special Populations

The effect of body weight on the pharmacokinetics of Follistim® was evaluated in a group of European and Japanese women who were significantly different in terms of body weight. The European subjects had a body weight of (mean \pm SD) 67.4 ± 13.5 kg and the Japanese subjects were 46.8 ± 11.6 kg. Following a single IM dose of 300 IU of Follistim®, the AUC (IU*h/L) was significantly smaller in European subjects (339 ± 105) than in Japanese subjects (544 ± 201). However, clearance per kg of body weight was essentially the same for the respective groups (0.014 and $0.013 \text{ l}\cdot\text{h}^{-1}\cdot\text{kg}^{-1}$). No pharmacokinetic studies have been conducted in other special populations.

Clinical Studies

Women

The efficacy of Follistim® was established in four controlled, clinical studies [three studies for Assisted Reproductive Technologies (ART) and one study for Ovulation Induction], three of which are described below. In these comparative studies, there were no clinically

significant differences between treatment groups in study outcomes.

Assisted Reproductive Technologies (ART)

Results from a randomized, assessor-blind, group comparative, multicenter safety and efficacy study of Follistim® (Protocol 37608) in 981 infertile women treated for one cycle with *in vitro* fertilization with Follistim® or Metrodin® after pituitary suppression with a GnRH agonist are summarized in Table 1.

Table 1. Results From a Randomized, Assessor-blind, Group Comparative, Multicenter Safety and Efficacy Study of Follistim® (Protocol 37608) in Infertile Women Treated With *In Vitro* Fertilization With Follistim® or Metrodin® After Pituitary Suppression With a GnRH Agonist¹

Parameter	Follistim® (n=585)	Metrodin® (n=396)
Total number of oocytes recovered	10.9	9.0
Number of mature oocytes recovered	9.1	7.3
Maximum serum estradiol before hCG (pmol/L) ²	6637	5692
Treatment duration (days)	11.0 (range 1-29)	11.6 (range 1-21)
Ongoing ³ pregnancy rate/attempt	22.2%	18.2%
Ongoing ³ pregnancy rate/transfer ⁴	26.0%	22.0%

¹ All values are means

² Conversion factor to pg/mL is 3.671

³ A single vital or multiple vital pregnancy was termed ongoing when a pregnancy, at least 12 weeks after embryo transfer (ET), was confirmed by the investigator

⁴ Transfers were limited to a maximum of three embryos

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- 1 The outcomes of the 286 clinical pregnancies (179 in Follistim® and 107 in Metrodin®) are
- 2 shown in Table 2:

Table 2. Outcome for All Clinical* Pregnancies

	Follistim® (n=179)	Metrodin® (n=107)
Did not result in live birth	50 (28%)	35 (33%)
Single birth	87 (49%)	43 (40%)
Multiple birth	42 (23%)	29 (27%)

*Clinical pregnancies included ongoing pregnancies as well as miscarriages with or without proof of a vital fetus

Results from a randomized, assessor-blind, group comparative, single center safety and efficacy study of Follistim® (Protocol 37604) in 89 infertile women treated with *in vitro* fertilization with Follistim® or Humegon® without pituitary suppression with a GnRH agonist are summarized in Table 3.

Table 3. Results From a Randomized, Assessor-blind, Group Comparative, Single Center Safety and Efficacy Study of Follistim® (Protocol 37604) in Infertile Women Treated With *In Vitro* Fertilization With Follistim® or Humegon® Without Pituitary Suppression With a GnRH Agonist¹

Parameter	Follistim® (n=54)	Humegon® (n=35)
Total number of oocytes recovered	9.9	7.6
Number of mature oocytes recovered	9.4	6.9
Maximum serum estradiol before hCG (pmol/L) ²	3791	3087
Treatment duration (days)	5.8 (range 1-9)	6.0 (range 2-10)
Ongoing ³ pregnancy rate/attempt	22.2%	17.1%
Ongoing ³ pregnancy rate/transfer ⁴	30.8%	22.2%

¹ All values are means

² Conversion factor to pg/mL is 3.671

³ A single vital or multiple vital pregnancy was termed ongoing when a pregnancy, at least 12 weeks after embryo transfer (ET), was confirmed by the investigator

⁴ Transfers were limited to a maximum of three embryos

The outcomes of the 22 clinical pregnancies (14 in Follistim® and 8 in Humegon®) are shown in Table 4:

Table 4. Outcome for all Clinical* Pregnancies

	Follistim®	Humegon®
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	(n=14)	(n=8)
Did not result in live birth	2 (14%)	2 (25%)
Single birth	7 (50%)	4 (50%)
Multiple birth	5 (36%)	2 (25%)

*Clinical pregnancies included ongoing pregnancies as well as miscarriages with or without proof of a vital fetus

Ovulation Induction

Results from a randomized, assessor-blind, group comparative, multicenter safety and efficacy study of Follistim® (Protocol 37609) in 172 chronic anovulatory women who failed to ovulate and/or conceive during clomiphene citrate treatment are summarized in Tables 5, 6, and 7.

Table 5. Cumulative Ovulation Rates from Protocol 37609

	Follistim® (n=105)	Metrodin® (n=67)
First treatment cycle	72%	63%
Second treatment cycle	82%	79%
Third treatment cycle	85%	82%

Table 6. Cumulative Ongoing¹ Pregnancy Rates from Protocol 37609

	Follistim® (n=105)	Metrodin® (n=67)
First treatment cycle	14%	10%
Second treatment cycle	19%	18%
Third treatment cycle	23%	19%

¹ All ongoing pregnancies were confirmed after at least 12 weeks after the hCG injection

The outcomes of the 56 clinical pregnancies (35 in Follistim® and 21 in Metrodin®) are shown in Table 7:

Table 7. Outcome for all Clinical* Pregnancies

	Follistim® (n=35)	Metrodin® (n=21)
Did not result in live birth	11 (31%)	8 (38%)
Single birth	22 (63%)	12 (57%)
Multiple birth	2 (6%)	1 (5%)

*Clinical pregnancies included ongoing pregnancies as well as miscarriages with or without proof of a vital fetus

Men

The safety and efficacy of Follistim[®] administered by SC injection concomitantly with Pregnyl[®] (Chorionic gonadotropin for injection, USP) has been examined in a clinical study for induction of spermatogenesis in hypogonadotropic hypogonadal men. The study compared the effects of two different Follistim[®]/Pregnyl[®] dosing schedules on semen parameters, serum levels of follicle stimulating hormone (FSH), and human chorionic gonadotropin (hCG), and assessed the local tolerance of the subcutaneous (SC) route of administration of both Follistim[®] and Pregnyl[®]. The multicenter study involved a sixteen-week pretreatment phase with Pregnyl[®] at a dosage of 1500 IU twice a week to normalize serum testosterone levels. In case of insufficient response after eight weeks of treatment (testosterone levels still below the lower reference range), the dose could be increased to 3000 IU twice a week. This phase was followed by a 48-week treatment phase. Patients who were still azoospermic after the pretreatment phase were randomized to receive either 225 IU Follistim[®] together with 1500 IU Pregnyl[®] twice a week or 150 IU Follistim[®] three times a week together with 1500 IU Pregnyl[®] twice weekly. Patients who required 3000 IU of Pregnyl[®] twice a week in the pretreatment phase were continued on that dosage during the treatment phase. The mean age of patients in the group receiving three weekly injections of Follistim[®] was 30.7 (range 18 to 47) years. In the group receiving two weekly injections of Follistim[®], the mean age was 30.1 (range 19 to 40) years. At baseline, mean left and right testis volumes were 4.61 ± 2.94 mL and 4.57 ± 3.00 mL, respectively in the group receiving three weekly injections of Follistim[®]. For the group receiving two weekly injections of Follistim[®], the mean left and right testis volumes were 6.54 ± 2.45 mL and 7.21 ± 2.94 mL, respectively at baseline. The primary efficacy endpoint was the percentage of men with a mean sperm density of $> 1 \times 10^6$ /mL on their last two treatment assessments.

Study 37618 Appendix

The outcomes of treatment in the 30 men enrolled in the treatment phase are summarized in Table 8:

Table 8. Number of Men Receiving Follistim® Who Achieved a Mean Sperm Density of $\geq 10^6$ /mL on Their Last Two Treatment Assessments

	Follistim® 150 IU three times a week (n=15)		Follistim® 225 IU twice a week (n=15)		Overall (n=30)	
	n	%	n	%	n	%
Sperm Density of $\geq 10^6$/mL						
Yes	6	40	7	47	13	43
No	9	60	8	53	17	57

In patients who demonstrated a sperm concentration of at least 10^6 per mL, this was achieved at a median time of 165 days after starting Follistim®, ranging from 25 to 327 days. For the 150 IU dose group the median time to reach a sperm concentration of at least 10^6 per mL was 186 days, ranging from 25 to 327 days. The median time before this was achieved in the 225 IU dose group was 141 days, ranging from 43 to 204 days. No pregnancy data were collected during the trial.

INDICATIONS AND USAGE

Women

Follistim® (follitropin beta for injection) is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Follistim® is also indicated for the induction of ovulation and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure.

Selection of Patients

Before treatment with Follistim® is instituted:

1. A thorough gynecologic and endocrinologic evaluation of the patient must be performed. The

evaluation should include a hysterosalpingogram (to rule out uterine and tubal pathology) and documentation of anovulation by means of reviewing a patient's history, performing a physical examination, determining serum hormonal levels as indicated, and optionally performing an endometrial biopsy. Patients with tubal pathology should receive Follistim® only if enrolled in an ART program.

2. Primary ovarian failure should be excluded by the determination of circulating gonadotropin levels.
3. Careful examination should be made to rule out early pregnancy.
4. Evaluation of the partner's fertility potential should be included in the workup procedure.

Men

Follistim® (follitropin beta 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

Before treatment with Follistim® is instituted for azoospermia:

1. A thorough medical and endocrinologic evaluation of the patient must be performed.
2. Hypogonadotropic hypogonadism should be confirmed and primary testicular failure should be excluded by the determination of circulating gonadotropin levels.
3. Prior to treatment with Follistim®, serum testosterone levels should be normalized with hCG.
4. Evaluation of the partner's fertility potential should be included in the workup procedure.

CONTRAINDICATIONS

Follistim® (follitropin beta for injection) is contraindicated in patients who exhibit:

1. Prior hypersensitivity to recombinant hFSH products.
2. A high circulating FSH level indicating primary gonadal failure.
3. Uncontrolled thyroid or adrenal dysfunction.
4. Tumor of the ovary, breast, uterus, testis, hypothalamus, or pituitary gland.
5. Pregnancy.
6. Heavy or irregular vaginal bleeding of undetermined origin.
7. Ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS).
8. Primary gonadal failure (ovarian or testicular).

WARNINGS

Follistim® (follitropin beta for injection) should be used only by physicians who are experienced in infertility treatment. Follistim® is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) (see WARNINGS-Overstimulation of the Ovary During Follistim® Therapy) with or without pulmonary or vascular complications (see WARNINGS-Pulmonary and Vascular Complications) and multiple births (see WARNINGS-Multiple Births). Gonadotropin therapy requires the availability of appropriate monitoring facilities (see PRECAUTIONS-Laboratory Tests).

Overstimulation of the Ovary During Follistim® Therapy

In order to minimize the hazards associated with the occasional abnormal ovarian enlargement that may occur with Follistim® therapy, the lowest effective dose should be used (see DOSAGE AND ADMINISTRATION). Use of ultrasound monitoring of ovarian response and/or measurement of serum estradiol levels can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Follistim® therapy, hCG should not be administered in this course of treatment; this will reduce the chances of developing Ovarian Hyperstimulation Syndrome (OHSS).

The Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical entity distinct from uncomplicated

ovarian enlargement and may progress rapidly to become a serious medical event. OHSS is characterized by a 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 OHSS developing are severe pelvic pain, nausea, vomiting and weight gain. The following symptoms have been reported in 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 WARNINGS-Pulmonary and Vascular Complications).

During clinical trials with Follistim® therapy, OHSS occurred in 53 (5.2%) of the 1,029 women treated and of these 29 (2.8%) were hospitalized. Cases of OHSS are more common, more severe, and more protracted if pregnancy occurs; therefore, patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and it can develop rapidly, reaching its maximum 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 serious OHSS occurs, treatment should be stopped and the patient should be hospitalized. Treatment is primarily symptomatic and should consist of bed rest, fluid and electrolyte management, and analgesics (if needed). Hemoconcentration associated with fluid loss into the peritoneal cavity, pleural cavity, and the pericardial cavity may occur and should be thoroughly assessed in the following manner: 1) fluid intake and output; 2) weight; 3) hematocrit; 4) serum and urinary electrolytes; 5) urine specific gravity; 6) BUN and creatinine; 7) total proteins with albumin: globulin ratio; 8) coagulation studies; 9)

electrocardiogram to monitor for hyperkalemia and 10) abdominal girth. These determinations should be performed daily or more often based on clinical need.

OHSS increases the risk of injury to the ovary. The ascitic, pleural, and pericardial fluid should not be removed unless there is the necessity to relieve symptoms such as pulmonary distress or cardiac tamponade. Pelvic examination may cause rupture of an ovarian cyst, which may result in hemoperitoneum, and should therefore be avoided. If bleeding occurs and requires surgical intervention, the clinical objective should be to control the bleeding and retain as much ovarian tissue as possible. Intercourse should be prohibited in patients with significant ovarian enlargement after ovulation because of the danger of hemoperitoneum resulting from ruptured ovarian cysts.

The management of OHSS may be divided into three phases: an acute, a chronic, and a resolution phase. Because the use of diuretics can accentuate the diminished intravascular volume, diuretics should be avoided except in the late phase of resolution as described below.

Acute Phase: Management during the acute phase should be directed at preventing hemoconcentration due to loss of intravascular volume to the third space and minimizing the risk of thromboembolic phenomena and kidney damage. Treatment is intended to normalize electrolytes while maintaining an acceptable but somewhat reduced intravascular volume. Full correction of the intravascular volume deficit may lead to an unacceptable increase in the amount of third space fluid accumulation.

Management includes administration of limited intravenous fluids, electrolytes, human serum albumin and strict monitoring of fluid intake and output. Monitoring for the development of hyperkalemia is recommended.

Chronic Phase: After stabilizing the patient during the acute phase, excessive fluid accumulation in the third space should be limited by instituting severe potassium, sodium, and fluid restriction.

Resolution Phase: A fall in hematocrit and an increasing urinary output without an increased intake are observed due to the return of the third space fluid to the intravascular compartment. Peripheral and/or pulmonary edema may result if the kidneys are unable to excrete third space fluid as rapidly as it is

mobilized. Diuretics may be indicated during the resolution phase, if necessary, to combat pulmonary edema.

Pulmonary and Vascular Complications

Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome) have been reported in women treated with gonadotropins. In addition, thromboembolic events both in association with, and separate from, the Ovarian Hyperstimulation Syndrome have been reported following gonadotropin therapy. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital 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 Follistim® treatment. The patient and her partner should be advised of the potential risk of multiple births before starting treatment. In clinical trials with Follistim® and Metrodin®, multiple gestation rates in ART patients were 31% and 38%, respectively, and in ovulation induction patients, the rates were 8% in both groups.

PRECAUTIONS

General

Careful attention should be given to the diagnosis of infertility and in the selection of candidates for Follistim® (follitropin beta for injection) therapy (see INDICATIONS AND USAGE - Selection of Patients).

Information for Patients

Prior to therapy with Follistim®, patients should be informed of the duration of treatment and monitoring procedures that will be required. The risks of Ovarian Hyperstimulation Syndrome and multiple births (see WARNINGS), and other possible adverse reactions (see ADVERSE REACTIONS) should be discussed.

Laboratory Tests

In most instances, treatment with Follistim® will result only in follicular growth and maturation. In order to complete the final phase of follicular maturation and to induce ovulation, hCG must be given following the administration of Follistim® or when clinical assessment of the patient indicates that sufficient follicular maturation has occurred. This may be directly estimated by sonographic visualization of the ovaries and endometrial lining and/or measuring serum estradiol levels. The combination of both ultrasonography and measurement of estradiol levels is useful for monitoring the growth and development of follicles, timing hCG administration, as well as minimizing the risk of OHSS and multiple gestations. The clinical evaluation of estrogenic activity (changes in vaginal cytology, changes in appearance and volume of cervical mucus, spinnbarkeit, and ferning of the cervical mucus) provides an indirect estimate of the estrogenic effect upon the target organs, and therefore it should only be used adjunctively with more direct estimates of follicular development (e.g., ultrasonography and serum estradiol determinations).

The clinical confirmation of ovulation is obtained by direct and indirect indices of progesterone production.

The indices most generally used are as follows:

- a) A rise in basal body temperature,
- b) Increase in serum progesterone, and
- c) Menstruation following the shift in basal body temperature.

When used in conjunction with 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:

- a) Fluid in the cul-de-sac,

- b) Follicle showing marked decrease in size, and
- c) Collapsed follicle.

Drug Interactions

No drug/drug interaction studies have been performed.

Carcinogenesis and Mutagenesis, Impairment of Fertility

Long-term toxicity studies in animals have not been performed with Follistim® to evaluate the carcinogenic potential of the drug. Follistim® was not mutagenic in the Ames test using *S. typhimurium* and *E. coli* tester strains and did not produce chromosomal aberrations in an *in vitro* assay using human lymphocytes.

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 Follistim®, 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.

Geriatric Use

Clinical studies of Follistim® did not include subjects aged 65 and over.

ADVERSE REACTIONS

Women

Assisted Reproductive Technologies (ART)

Rates of adverse events from a randomized, assessor-blind, group comparative, multicenter safety and efficacy study of Follistim® (Protocol 37608) in 989 infertile women treated with *in vitro* fertilization with Follistim® or Metrodin® after pituitary suppression with a GnRH agonist are summarized in Table 9.

Table 9. Incidence of Adverse Clinical Experiences (>1%) that Occurred in Protocol 37608

Adverse Event	Follistim® (n=591)	Metrodin® (n=398)
Miscarriage	11.0%	11.3%
Ovarian Hyperstimulation Syndrome	5.2%	4.3%
Ectopic pregnancy	3.0%	3.8%
Abdominal pain	2.5%	2.3%
Injection site pain	1.7%	0.5%
Vaginal hemorrhage	1.5%	0.8%

Ovulation Induction

Rates of adverse events from a randomized, assessor-blind, group comparative, multicenter safety and efficacy study of Follistim® (Protocol 37609) in 172 chronic anovulatory women who failed to ovulate and/or conceive during clomiphene citrate treatment are summarized in Table 10.

Table 10. Incidence of Adverse Clinical Experiences (>1%) that Occurred in Protocol 37609

Adverse Event	Follistim® (n=105)	Metrodin® (n=67)
Miscarriage	9.5%	9.0%
Ovarian Hyperstimulation Syndrome	7.6%	4.5%
Abdominal discomfort	2.9%	1.5%
Abdominal pain, lower	2.9%	1.5%
Abdominal pain	1.9%	3.0%
Ovarian cyst	2.9%	3.0%

The following adverse events have been reported in women treated with gonadotropins: pulmonary and vascular complications (see WARNINGS), hemoperitoneum, adnexal torsion (as a complication of ovarian enlargement), dizziness, tachycardia, dyspnea, tachypnea, febrile reactions, flu-like symptoms including

fever, chills, musculoskeletal aches, joint pains, nausea, headache and malaise, breast tenderness, and dermatological symptoms (dry skin, body rash, hair loss and hives).

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 Follistim[®] (follitropin beta for injection) was examined in a clinical trial that enrolled 49 patients for induction of spermatogenesis, of whom 30 received Follistim[®]. Two subjects in the treatment period each reported one serious adverse event, which were judged not related to study drug by the investigator. The events involved a pilonidal cyst and hemorrhoids. Both subjects recovered from their adverse events. In the Follistim[®] treatment phase, no patients discontinued due to an adverse event. In total 21 patients in the treatment phase experienced at least one adverse event. Nine were judged by the investigator to be possibly related to study drug and these included: two cases of acne, two cases of injection site reaction, two cases of injection site pain, and single cases of varicose veins, gynecomastia, and a dermoid cyst.

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The local tolerance data were comparable between the two treatment groups. The mean percentage of days without pain calculated for all subjects in the treatment period was 91.3% for patients in the 150 IU (three times a week) and 76.0% for patients in the 225 IU (two times a week) Follistim[®] treatment groups. In the 225 IU (twice per week) group, local symptoms judged as severe by the investigator were: itching in one patient, pain in two patients, swelling in two patients, and redness in one patient. In the 150 IU (three times per week) group, one event in one patient (bruising) was judged as severe. No patient discontinued treatment due to injection site reaction or injection site pain.

DRUG ABUSE AND DEPENDENCE

There have been no reports of abuse or dependence with Follistim[®] (follitropin beta for injection).

OVERDOSAGE

Aside from the possibility of Ovarian Hyperstimulation Syndrome (see WARNINGS-Overstimulation of the Ovary During Follistim[®] Therapy) and multiple gestations (see WARNINGS-Multiple Births), there is no additional information concerning the consequences of acute overdose with Follistim[®] (follitropin beta for injection).

DOSAGE AND ADMINISTRATION

Women

Assisted Reproductive Technologies (ART)

A starting dose of 150 to 225 IU of Follistim[®] (follitropin beta for injection) is recommended for at least the first four days of treatment. After this, the dose may be adjusted for the individual patient based upon their ovarian response. In clinical studies with patients who are responding, it was shown that daily maintenance dosages ranging from 75 to 300 IU for six to twelve days are sufficient, although longer treatment may be necessary. However, in patients that were low or poor responders, maintenance doses of 375 to 600 IU were administered according to individual response. This later category comprised approximately 10% of the women evaluated during clinical studies. The maximum, individualized, daily

dose of Follistim® that has been used in clinical studies is 600 IU. When a sufficient number of follicles of adequate size are present, the final maturation of the follicles is induced by administering hCG at a dose of 5,000 IU to 10,000 IU. Oocyte (egg) retrieval is performed 34 to 36 hours later. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of Follistim® therapy; this will reduce the chance of developing OHSS.

Ovulation Induction

There are a variety of treatment protocols available for ovulation induction. In studies using Follistim®, a stepwise gradually increasing dosing scheme was used. The starting dose was 75 IU of Follistim® for up to 14 days. The dose was then increased by 37.5 IU of Follistim® at weekly intervals until follicular growth and/or serum estradiol levels indicated an adequate response. The maximum, individualized, daily dose of Follistim® that has been safely used for ovulation induction patients during clinical trials is 300 IU. The patient should be treated until ultrasonic visualizations and/or serum estradiol determinations indicate pre-ovulatory conditions equivalent to or greater than those of the normal individual followed by hCG, 5,000 IU to 10,000 IU. If the ovaries are abnormally enlarged on the last day of Follistim® therapy, hCG must be withheld during this course of treatment; this will reduce the chances of developing OHSS. During treatment with Follistim® and during a two week post-treatment period, patients should be examined at least every other day for signs of excessive ovarian stimulation. It is recommended that Follistim® administration be stopped if the ovaries become abnormally enlarged or abdominal pain occurs. Most OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation.

For ovulation induction, the couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent from the indices employed for the

determination of progestational activity (see PRECAUTIONS-Laboratory Tests). Care should be taken to insure insemination. In the light of the foregoing 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 these necessary laboratory studies, he/she should not use Follistim®.

Men

Male Patients with Hypogonadotropic Hypogonadism

Follistim® must be given by SC injection concurrently with hCG treatment. Prior to concomitant therapy with Follistim® and hCG, pretreatment with hCG alone is required. The initial dosage of hCG should be 1500 IU twice a week to normalize serum testosterone levels. In case of insufficient response after eight weeks of treatment (testosterone levels still below the lower reference range), the dose could be increased to 3000 IU twice a week. After normal serum testosterone levels have been reached, Follistim® should be given at a dosage of 450 IU/week, as either 225 IU twice per week or 150IU three times per week, in combination with hCG. The dosage of hCG should continue at the same dose used to normalize testosterone levels. The combined treatment should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a patient has not responded after this period, the combination therapy may be continued . Treatment response was noted at up to 12 months.

Directions for using Follistim®

1. Wash hands thoroughly with soap and water.
2. Before injections, the septum tops of the vials should be wiped with an aseptic solution to prevent contamination of the contents.
3. To prepare the Follistim® solution, inject 1 mL of Sterile Water for Injection, USP into the vial of Follistim®. **DO NOT SHAKE**, but gently swirl until the solution is clear. Generally, the Follistim® dissolves immediately. Check the liquid in the container. If it is not clear or has

particles in it, **DO NOT USE IT.**

4. For patients requiring a single injection from multiple vials of Follistim®, up to 4 vials can be reconstituted with 1 mL of Sterile Water for Injection, USP. This can be accomplished by reconstituting a single vial as described above (see step 3). Then draw the entire contents of the first vial into a syringe, and inject the contents into a second vial of lyophilized Follistim®. Gently swirl the second vial, as described above, once again checking to make sure the solution is clear and free of particles. This step can be repeated with 2 additional vials for a total of up to 4 vials of lyophilized Follistim® into 1 mL of diluent.
5. a) For Women:
Immediately ADMINISTER the reconstituted Follistim® either SUBCUTANEOUSLY (SC) or INTRAMUSCULARLY (IM). Any unused reconstituted material should be discarded.
b) For Men:
Immediately ADMINISTER the reconstituted Follistim® SC only. Any unused reconstituted material should be discarded.
6. Draw the reconstituted Follistim® into an empty, sterile syringe.
7. Hold the syringe pointing upwards and gently tap the side to force any air bubbles to the top; then squeeze the plunger gently until all the air has been expelled and only Follistim® solution is left in the syringe.
8. The injection site should be swabbed with a disinfectant to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.

The most convenient sites for SC injection are either in the abdomen around the navel where there

is a lot of loose skin and layers of fatty tissue or in the upper thigh. Pinch up a large area of skin between the finger and thumb. You should vary the injection site a little with each injection. The needle should be inserted at the base of the pinched-up skin at an angle of 45° to the skin surface. The best site for IM injection of Follistim® is the upper outer quadrant of the buttock muscle. This area contains a large volume of muscle with few blood vessels and major nerves. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution disperse correctly. The needle should be inserted right up to the hilt at an angle of 90° to the skin surface. Pushing in with a quick thrust causes the least discomfort.

9. If the needle is correctly positioned it will be difficult to draw back on the plunger. Any blood drawn into the syringe means the needle tip has penetrated a vein or artery. If this happens, remove the syringe, cover the injection site with a swab containing disinfectant and apply pressure; the site should stop bleeding in a minute or two.
10. Once the needle is properly placed, depress the plunger **slowly** and steadily, so the solution is correctly injected and the skin or muscle tissue is not damaged.
11. Pull the syringe out quickly and apply pressure to the site with a swab containing disinfectant. A gentle massage of the site—while still maintaining pressure—helps disperse the Follistim® solution and relieve any discomfort.
12. Use the disposable syringe only once and dispose of it properly.

HOW SUPPLIED

Follistim® (follitropin beta for injection) is supplied in a sterile, freeze-dried form, as a white to off-white cake or powder in vials containing 75 IU of FSH activity. The following package combinations are available:

- 1 vial 75 IU Follistim® and 1 vial 5 mL Sterile Water for Injection, USP.
NDC 0052-0306-18
- 5 vials 75 IU Follistim® and 5 vials 5 mL Sterile Water for Injection, USP.

NDC 0052-0306-31

Storage

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

Rx only



Manufactured by
Organon Inc.
West Orange, NJ 07052
Diluent manufactured by
Luitpold Pharmaceuticals, Inc.
Shirley, NY 11967

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this page is the manifestation of the electronic signature.**

/s/

Shelley Slaughter
2/7/02 05:32:56 PM
Shelley R. Slaughter, Acting Deputy Director, for Daniel Shames,
Acting Director