

Follistim[®] AQ Cartridge

(follitropin beta injection)

FOR SUBCUTANEOUS USE ONLY

DESCRIPTION

Follistim[®] AQ Cartridge (follitropin beta injection) contains human follicle-stimulating hormone (hFSH), a glycoprotein hormone which is manufactured by recombinant DNA (rDNA) technology. The active drug substance, 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 activity.¹ 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 follitropin beta are indistinguishable from that of human follicle-stimulating hormone (hFSH) of urinary source. Also, based on available data derived from physiochemical tests and bioassay, follitropin beta and follitropin alfa, another recombinant follicle-stimulating hormone product, are indistinguishable.

Follistim[®] AQ Cartridge is a ready-for-use, prefilled with solution, disposable cartridge containing either 175 IU of follitropin beta in 0.210 mL (833 IU/mL), 350 IU in 0.420 mL (833 IU/mL), 650 IU in 0.780 mL (833 IU/mL) or 975 IU in 1.170 mL (833 IU/mL) of aqueous solution for multiple dose use, with a maximal deliverable dose of either **150 IU, 300 IU, 600 IU or 900 IU**, respectively. Inactive ingredients in the cartridges include: benzyl alcohol, NF 10 mg/mL; L-methionine, USP 0.5 mg/mL; polysorbate 20, NF 0.2 mg/mL; sodium citrate (dihydrate), USP 14.7 mg/mL; sucrose, NF 50 mg/mL; and water for injection, USP. Hydrochloric acid, NF and/or sodium hydroxide, NF are used to adjust the pH to 7.

Follistim[®] AQ Cartridge is for use only with the Follistim Pen[®], which features an adjustable dosing system for administering the drug in a microvolume of solution. The Follistim Pen[®] with Follistim[®] AQ Cartridge is intended for SUBCUTANEOUS USE ONLY. The recombinant protein in Follistim[®] AQ Cartridge 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[®] AQ Cartridge may contain up to 11% of oxidized follitropin beta.

In clinical trials with Follistim[®] (follitropin beta for injection), 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 (ϵ_{277} :mg⁻¹cm⁻¹) = 1.066.

CLINICAL PHARMACOLOGY

Follicle stimulating hormone (FSH), the active component in Follistim[®] AQ Cartridge (follitropin beta injection), is required for normal follicular growth, maturation, and gonadal steroid production. In women, 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. Follistim[®] AQ Cartridge stimulates ovarian follicular growth in women who do not have primary ovarian failure. 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 treatment with Follistim[®] AQ Cartridge when patient monitoring indicates appropriate follicular development parameters have been reached.

Pharmacokinetics

The pharmacokinetics of Follistim[®] AQ Cartridge (follitropin beta injection) were evaluated in an open-labeled, single-center, randomized study in 20 healthy female subjects. A single subcutaneous injection of lyophilized Follistim[®] (follitropin beta for injection) which was reconstituted and administered by conventional syringe was compared to a single subcutaneous injection of Follistim[®] AQ Cartridge administered using the Follistim Pen[®]. The precision of the Follistim Pen[®] resulted in more efficient delivery of the ready-for-use solution contained in the Follistim[®] AQ Cartridge and an 18% increase in AUC_{0-∞} and C_{max}. The 18% difference found between serum FSH concentrations in subjects administered the two formulations was due to differences between the anticipated and actual volume delivered with the conventional syringe. The pharmacokinetic parameters for Follistim[®] AQ Cartridge are as follows:

TABLE 1: Mean (SD) Pharmacokinetic Parameters of a Single Subcutaneous Injection of 150 IU of Follistim[®] AQ Cartridge (n=20)

	AUC _{0-∞} (IU/L*h)	C _{max} (IU/L)	t _{max} (h)	t _{1/2} (h)	CL _{app} (L/h/kg)
Follistim [®] AQ Cartridge	215.1 (45.8)	3.4 (0.7)	12.9 (6.2)	33.4 (4.2)	0.01 (0.003)

AUC _{0-∞}	Area under the curve
C _{max}	Maximum concentration
t _{max}	Time to maximum concentration
t _{1/2}	Elimination half life
CL _{app}	Clearance

Absorption

The bioavailability of Follistim[®] following subcutaneous administration was investigated in healthy, pituitary-suppressed, female subjects given a single 300 IU dose. After subcutaneous injection the apparent dose absorbed was 77.8%.

In healthy, pituitary-suppressed, female subjects following a subcutaneous administration of 300 IU of Follistim[®], the AUC was 455.6 ± 141.4 IU/L*h and C_{\max} was 5.41 ± 0.72 IU/L. A multiple, dose proportionality, pharmacokinetic study of Follistim[®] was completed in healthy, pituitary-suppressed, female subjects given subcutaneous doses of 75, 150, or 225 IU for seven days. Steady-state blood concentrations of FSH were reached with all doses after five days of treatment based on the minimum concentrations of FSH just prior to dosing (C_{\min}). Peak blood concentrations with the 75, 150, and 225 IU dose were 4.30 ± 0.60 , 8.51 ± 1.16 , and 13.92 ± 1.81 IU/L, respectively.

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[®] AQ Cartridge is biochemically similar to natural FSH, and it is therefore anticipated that it is metabolized in the same manner.

Elimination

The elimination half-life ($t_{1/2}$) following a single subcutaneous injection of 150 IU of Follistim[®] AQ Cartridge in female patients was 33.4 (4.2) hours. The clearance was 0.01 (0.003) L/h/kg.

Special Populations

The pharmacokinetics of Follistim[®] AQ Cartridge (follitropin beta injection) have not been determined in special populations such as geriatric, pediatric, renally impaired, and hepatically impaired patients.

Drug-Drug Interactions

Formal drug-drug interaction studies have not been conducted (see PRECAUTIONS).

Clinical Studies

The efficacy, tolerance, and ease of use of Follistim[®] AQ Cartridge (follitropin beta injection) administered using the Follistim Pen[®] were established in two US clinical studies [one study for Assisted Reproductive Technologies (ART) and one study for Ovulation Induction (OI)].

Assisted Reproductive Technologies (ART)

Results from an open-label, non-controlled, multi-center study in 60 women undergoing Controlled Ovarian Hyperstimulation (COH) for IVF or ICSI with Follistim[®] AQ Cartridge are summarized in Table 2.

TABLE 2: Results from an Open-label, Non-controlled, Multi-center Study in 60 Women Undergoing COH for IVF or ICSI with Follistim® AQ Cartridge Self-Administered With the Follistim Pen®.

Parameter	Follistim® AQ Cartridge n=60
Mean(SD) number of oocytes recovered	13.9(10.3)
Mean(SD) total number of embryos obtained	7.2(5.5)
Median serum estradiol on the day of hCG (pg/mL)	1423.0 Range (469.5-4874.0)
Mean(SD) treatment duration (days)	9.0 (1.6)
Biochemical pregnancy rate/attempt (%)	56.7
Biochemical pregnancy rate/transfer (%)	61.8

Ovulation Induction (OI)

Results from an open-label, non-controlled, multicenter study in 43 clomiphene-resistant women with chronic anovulation (WHO group II) who were treated with Follistim® AQ Cartridge for induction of ovulation are summarized in Table 3.

TABLE 3: Results from an Open-label, Non-controlled, Multicenter Study in 43 Clomiphene- resistant Women with Chronic Anovulation (WHO group II) Undergoing Ovulation Induction with Follistim® AQ Cartridge Self-Administered with the Follistim Pen®.

	Follistim® AQ Cartridge (n = 43)	n
Ovulation rate	95.3%	41
Biochemical pregnancy per attempt	34.9%	15

Ease of Use

In an observer questionnaire, designed to assess the "Ease of Use" of Follistim® AQ Cartridge with the Follistim Pen®, subjects rated their experience with the pen injector device. Subjects undergoing ART and OI rated their injection experience in two separate studies. On Day 6 in the ART group, more subjects rated the overall experience as "very good" as compared to Day 2, 54 subjects (90%) versus 49 subjects (81.8%), respectively and only one subject (1.7%) had a "neutral" response. In the Ovulation Induction group, the experience rating of "very good" increased from 90.7% on Day 2 to 95.2% on Day 8.

INDICATIONS AND USAGE

Follistim® AQ Cartridge (follitropin beta injection) is indicated for the development of multiple follicles in ovulatory patients participating in an Assisted Reproductive Technology (ART) program. Follistim® AQ Cartridge 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[®] AQ Cartridge (follitropin beta injection) is initiated:

- 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[®] AQ Cartridge 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.

CONTRAINDICATIONS

Follistim[®] AQ Cartridge (follitropin beta injection) is contraindicated in women who exhibit:

- 1) Prior hypersensitivity to recombinant hFSH products
- 2) A high circulating FSH level indicating primary ovarian failure
- 3) Uncontrolled thyroid or adrenal dysfunction
- 4) Tumor of the ovary, breast, uterus, 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) Hypersensitivity reactions to streptomycin or neomycin. Follistim[®] AQ Cartridge may contain traces of these antibiotics and may cause hypersensitivity reactions in susceptible persons.

WARNINGS

Follistim[®] AQ Cartridge (follitropin beta injection) should be used only by physicians who are experienced in infertility treatment. Changes in brand (manufacturer), type (recombinant, urinary, etc.), and/or method of administration (Follistim Pen[®], conventional syringe, etc.) may result in the need to adjust the dose. Follistim[®] AQ Cartridge administered with the Follistim Pen[®] contains a potent gonadotropic substance and delivers on average an 18% higher amount of follitropin beta as compared to lyophilized preparations administered by conventional syringe. Accordingly, a lower starting dose for gonadotropin stimulation and dose adjustments during gonadotropin stimulation should be considered for each woman treated with Follistim[®] AQ Cartridge (see DOSAGE AND ADMINISTRATION).

Overstimulation of the Ovary During Treatment with Follistim[®] AQ Cartridge (follitropin beta injection)

In order to minimize the hazards associated with the occasional abnormal ovarian enlargement that may occur with Follistim[®] AQ Cartridge 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 treatment with Follistim[®] AQ Cartridge, hCG should not be administered in this course of treatment, to reduce the chances of developing Ovarian Hyperstimulation Syndrome (OHSS).

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[®] (follitropin beta for injection) and Follistim[®] AQ Cartridge (follitropin beta injection) therapy, OHSS occurred in 60 (5.3%) of the 1132 women treated and of these 33 (2.9%) 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 Multiple births have been reported for all FSH treatments including Follistim[®] (follitropin beta for injection) treatment. The patient and her partner 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 and in the selection of candidates for treatment with Follistim[®] AQ Cartridge (follitropin beta injection) (see INDICATIONS AND USAGE - Selection of Patients).

Information for Patients

Physicians must instruct patients on the correct usage and dosing of Follistim[®] AQ Cartridge in conjunction with the Follistim Pen[®].

Patients should read and follow all instructions in the Follistim Pen[®] Instructions for Use Manual/Treatment Diary prior to administration of Follistim[®] AQ Cartridge.

Prior to treatment with Follistim[®] AQ (follitropin beta injection) Cartridge, 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[®] AQ Cartridge (follitropin beta injection) 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[®] AQ Cartridge 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
- 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
- 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[®] AQ Cartridge (follitropin beta injection) to evaluate the carcinogenic potential of the drug. Follistim[®] (follitropin beta for injection) 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[®] AQ Cartridge (follitropin beta injection), 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 did not include subjects aged 65 and over.

ADVERSE REACTIONS

Assisted Reproductive Technologies (ART)

Rates of adverse events from an open-label, non-controlled, multicenter study in 60 women undergoing COH for IVF or ICSI with Follistim[®] AQ Cartridge administered with the Follistim Pen[®] are summarized in Table 4

TABLE 4: Incidence of Adverse Clinical Experiences (≥5%)

Adverse Event	Follistim® AQ Cartridge n=60
Abdominal pain	28%
Flatulence	27%
Abdominal pain, gynecological	25%
Nausea	17%
Breast pain, female	15%
Injection site reaction	10%
Abdomen enlarged	8%
Back pain	7%
Constipation	5%
Headache	5%
Ovarian pain	5%

Ovulation Induction

Rates of adverse events from an open-label, non-controlled, multicenter study in 43 clomiphene- resistant women with chronic anovulation (WHO group II) undergoing Ovulation Induction with Follistim® AQ Cartridge administered with the Follistim Pen® are summarized in Table 5.

TABLE 5: Incidence of Adverse Clinical Experiences (≥5%)

Adverse Event	Follistim® AQ Cartridge n=43
Ovarian hyperstimulation syndrome	9%
Abdominal pain	5%
Injection site reaction	5%
Sinusitis	5%
Upper respiratory tract infection	5%

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, erythema, 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.

Congenital Anomalies The incidence of congenital malformations after Assisted Reproductive Technologies (ART) may be slightly higher than after spontaneous conception. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, sperm characteristics) and to the higher incidence of multiple gestations after ART. There are no indications that the use of gonadotropins, during ART is associated with an increased risk of congenital malformations.

DRUG ABUSE AND DEPENDENCE There have been no reports of abuse or dependence with Follistim® AQ Cartridge (follitropin beta injection).

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

When administering Follistim® AQ Cartridge (follitropin beta injection), a lower starting dose for gonadotropin stimulation and dose adjustments during gonadotropin stimulation should be considered for each patient. For that purpose the following Dose Conversion Table might be a useful reference.

**TABLE 6: Follistim® AQ Cartridge Administered With
the Follistim Pen® Dose Conversion Table***

Lyophilized recombinant FSH dosing in ampules or vials, using conventional syringe	Follistim® AQ Cartridge dosing with the Follistim Pen®
75 IU	50 IU
150 IU	125 IU
225 IU	175 IU
300 IU	250 IU
375 IU	300 IU
450 IU	375 IU

***Each value represents an 18% difference rounded to the nearest 25 IU increment.**

Follistim® AQ Cartridge (follitropin beta injection) is delivered by the Follistim Pen® which accurately delivers the dose to which it is set. In a clinical bioavailability study that compared administration of the dissolved lyophilized follitropin beta preparation using a conventional syringe and needle and a ready-to-use follitropin beta solution in a cartridge injected with the pen device, it was shown that the pen device delivered, on average of an 18% higher amount of follitropin beta.

This difference is due to the accurate dosing obtained with the Follistim Pen[®] compared to a conventional syringe. This 18% difference corresponds to a similar difference in serum FSH concentrations caused by differences between the anticipated and the actual volume of follitropin beta injected with the conventional syringe.

The net deliverable dose of 150 IU, 300 IU, 600 IU and 900 IU are based upon a maximum of two injections of 75 IU (for 150 IU), four injections of 75 IU (for 300 IU), six injections of 100 IU (for 600 IU) and nine injections of 100 IU (for 900 IU).

Assisted Reproductive Technologies (ART)

In an open-label, non-controlled, multicenter study, 60 women who were undergoing COH for IVF with and without ICSI were treated with Follistim[®] AQ Cartridge at a starting dose of 150 to 225 IU for the first 5 days of treatment. This dose could be adjusted after that time based upon ovarian response. The maximum, individualized, daily dose of Follistim[®] AQ Cartridge used in this clinical study was 450 IU.

A starting dose of 150 to 225 IU or lower of Follistim[®] AQ Cartridge (follitropin beta injection) is recommended for at least the first 5 days of treatment. If a prescriber generally uses a starting dose of 150 to 225 IU of lyophilized gonadotropin, then the prescriber should consider using a lower starting dose of Follistim[®] AQ Cartridge. (See dose Conversion Table). After this, the dose may be adjusted for the individual patient based upon her ovarian response. For Follistim[®] AQ Cartridge, lower maintenance doses should be considered for each patient.

During treatment with Follistim[®] AQ Cartridge, 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 5000 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 treatment with Follistim[®] AQ Cartridge. This will reduce the chance of developing OHSS.

Ovulation Induction

In an open-label, non-controlled, multi-center study in 43 clomiphene-resistant women with chronic anovulation (WHO group II) who were treated with Follistim[®] AQ Cartridge for induction of ovulation, a stepwise increasing dose regimen was included. The starting dose was 75 IU of Follistim[®] AQ Cartridge (follitropin beta injection) for up to 7 days. The dose was increased by either 25 IU or 50 IU at weekly intervals until follicular growth and/or serum estradiol levels indicated an adequate ovarian response. The maximum, individualized daily dose of Follistim[®] AQ Cartridge that had been used for ovulation induction patients during this clinical trial is 175 IU.

A starting dose of 75 IU or lower of Follistim[®] AQ Cartridge (follitropin beta injection) is recommended for at least the first 7 days of treatment with dose adjustments at weekly intervals based upon patient response. If a prescriber generally uses a starting dose of 75

IU of lyophilized gonadotropin, then the prescriber should consider using a lower starting dose of Follistim[®] AQ Cartridge (See Dose Conversion Table).

Treatment should continue 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, 5000 to 10,000 IU. If the ovaries are abnormally enlarged on the last day of treatment with Follistim[®] therapy, hCG must be withheld during this course of treatment; this will reduce the chances of developing OHSS.

During treatment with Follistim[®] AQ Cartridge (follitropin beta injection) 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 treatment with Follistim[®] AQ Cartridge 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[®] AQ Cartridge.

Parenteral drug products should be inspected visually for particulate matter and clarity prior to administration whenever solution and container permit. Do not use solution if particulate matter is present.

No other drugs should be added or combined into the Follistim[®] AQ Cartridge.

HOW SUPPLIED

Follistim[®] AQ Cartridge (follitropin beta injection) is supplied in a box containing disposable, 29 gauge, ultra-fine, 1/2 -inch, sterile BD Micro-Fine[™] Pen Needles (for use with Follistim Pen[®] available separately) and one disposable, blister packed, prefilled 1.5 mL colorless glass cartridge, with grey rubber piston and an aluminum crimp-cap with black rubber inlay and in the following presentations:

- NDC 0052-0303-01 Follistim[®] AQ Cartridge 175 IU/0.210 mL (delivering 150 IU) with orange crimp-caps and 3 BD Micro-Fine[™] Pen Needles
- NDC 0052-0313-01 Follistim[®] AQ Cartridge 350 IU/0.420 mL (delivering 300 IU) with silver crimp-caps and 5 BD Micro-Fine[™] Pen Needles
- NDC 0052-0316-01 Follistim[®] AQ Cartridge 650 IU/0.780 mL (delivering 600 IU) with gold crimp-caps and 7 BD Micro-Fine[™] Pen Needles

NDC 0052-0326-01 Follistim® AQ Cartridge 975 IU/1.170 mL (delivering 900 IU)
with blue crimp-caps and 10 BD Micro-Fine™ Pen Needles

Storage

Store refrigerated, 2-8° C (36-46° F) until dispensed. Upon dispensing, the product may be stored by the patient at 2-8° C (36-46° F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber stopper of the Follistim® AQ Cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2-25°C (36-77°F). Protect from light. Do not freeze.

For more information, call 1-866-836-5633

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BD Micro-Fine™ is a trademark of Becton, Dickinson and Company

R_x only



Manufactured for Organon USA Inc.
West Orange, NJ 07052
by Vetter Pharma-Fertigung GmbH & Co. KG
Ravensburg, Germany
and packaged by Organon (Ireland) Ltd., Swords
Co. Dublin, Ireland

PATIENT INFORMATION LEAFLET

Follistim[®] AQ Cartridge

(follitropin beta injection)

Follistim[®] AQ Cartridge

150 IU, 300 IU, 600 IU and 900 IU

Read the patient information carefully before you start using Follistim[®] AQ (fol-i-stim) Cartridge (follitropin beta injection) with Follistim Pen[®] and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare professional about your medical condition or treatment.

What is Follistim[®] AQ Cartridge?

Follistim[®] AQ Cartridge (follitropin beta injection) is a medicine that contains the hormone follicle stimulating hormone (FSH). FSH may help (stimulate) the ovaries to make eggs in women who have fertility problems. FSH will not help women who have a condition called primary ovarian failure.

What is Follistim[®] AQ Cartridge used for?

Follistim[®] AQ Cartridge (follitropin beta injection) is used:

- a. To help women who have problems with ovulation. Follistim[®] AQ Cartridge will not help women whose ovaries do not work at all (primary ovarian failure).
- b. For women that are in an Assisted Reproductive Technology (ART) program, such as *in vitro* fertilization.

If you have previously used gonadotropins, your dose may be different with Follistim[®] AQ Cartridge. **Always follow your healthcare professional's dosing instructions when administering Follistim[®] AQ Cartridge. Your healthcare professional has individualized the dose to be administered based on your medical history. Do not change your dose unless instructed by your healthcare professional.**

Who should not take Follistim[®] AQ Cartridge?

Do not use Follistim[®] AQ Cartridge (follitropin beta injection) if you:

- are allergic to recombinant human FSH products (see the end of this leaflet for a list of all the ingredients in Follistim[®] AQ Cartridge)
- have primary ovarian failure (your ovaries do not work at all)
- are pregnant, or think you might be pregnant
- have uncontrolled thyroid or adrenal gland problems
- have tumors in your ovaries, breasts, uterus, hypothalamus, or pituitary gland

- have heavy or irregular vaginal bleeding and the cause is not known
- have ovarian cysts or enlarged ovaries, not due to polycystic ovary syndrome (PCOS)
- are allergic to streptomycin or neomycin. Follistim[®] AQ Cartridge may contain traces of these antibiotics and may cause allergic reactions

Tell your healthcare professional if you are breast feeding. It is not known if Follistim[®] AQ passes into your milk.

What are the possible side effects of Follistim[®] AQ Cartridge?

Follistim[®] AQ Cartridge (follitropin beta injection) may cause serious side effects. This can happen if too much Follistim[®] AQ Cartridge is used or it is not used the right way.

- **Ovarian Hyperstimulation Syndrome (OHSS).** OHSS is a serious medical problem that can happen when the ovaries are overstimulated. In rare cases it has caused death. OHSS causes fluid to build up suddenly in the stomach and chest areas. OHSS may occur after treatment with Follistim[®] AQ Cartridge.

Call your healthcare professional right away if you get any of the following symptoms:

- severe pelvic pain (lower stomach area)
- nausea
- vomiting
- sudden weight gain
- reduced urine output

- **Lung and blood vessel problems.** Follistim[®] AQ Cartridge and other FSH products may cause serious lung problems including fluid in the lungs (atelectasis) and acute respiratory distress syndrome (ARDS). Follistim[®] AQ Cartridge and other FSH products may also cause blood clots in blood vessels. This can lead to blood vessel problems (thrombophlebitis), stroke, loss of limb, or a blood clot in the lung (pulmonary embolus).

- **Multiple births.** Follistim[®] AQ Cartridge and other FSH products can cause multiple births. Your healthcare professional will discuss your chances of multiple births.

- Other side effects with Follistim[®] AQ Cartridge include stomach pain, gas, pelvic pain, nausea, breast pain, injection site problems, enlarged stomach area, back pain, constipation, headache and ovarian pain. If you get any side effects that concern you, call your healthcare professional.

These are not all the side effects of Follistim[®] AQ Cartridge. Contact your doctor or other healthcare professional without delay if you are experiencing symptoms including significant abdominal pain, or if symptoms develop some days after the last injection has been given (see “Who should not take Follistim[®] AQ Cartridge?”).

How should I use Follistim[®] AQ Cartridge?

- Your healthcare professional will decide on the dose of Follistim[®] AQ Cartridge (follitropin beta injection) that is best for you. This dose may be increased or decreased as your treatment goes on. This will depend on your type of treatment. It is very important that you follow your healthcare professional’s instructions exactly.
- Follistim[®] AQ Cartridge is given by an injection just under the skin (subcutaneous injection).

Your healthcare professional's office will teach you how to inject yourself. See the end of this leaflet for "INSTRUCTIONS FOR USE". Do not inject Follistim® AQ Cartridge at home until your healthcare professional's office has taught you the right way.

Close care by your healthcare professional is very important. Usually, ultrasound scans (special x-rays) of the ovaries are regularly made. Blood or urine samples are regularly taken. The results of these tests allow your healthcare professional to choose the right dose of Follistim® AQ Cartridge for you each day. This is very important. Too high a dose of FSH may lead to rare, but serious problems in which the ovaries become overstimulated (too active). This may be noticed as pain in the abdomen (stomach area). Regular checking of your response to FSH treatment helps your healthcare professional lower your chances of ovarian overstimulation. Call your healthcare professional right away if you get strong abdominal pain. Also call your healthcare professional right away if this happens some days after the last injection has been given.

Dosage

• **Assisted Reproductive Technologies (ART)**

A starting dose of Follistim® AQ Cartridge (follitropin beta injection) will be prescribed by your healthcare professional based upon review of your medical history. This starting dose of Follistim® AQ Cartridge to be injected with the Follistim Pen® under the skin is usually recommended for at least the first 5 days of treatment. After this, your healthcare professional may adjust your dose based upon how your ovaries are responding to Follistim® AQ Cartridge. When an ultrasound examination shows that you are ready, another drug (hCG) may be injected to induce the final maturation of the follicles.

• **Ovulation Induction (OI)**

A starting dose of Follistim® AQ Cartridge (follitropin beta injection) will be prescribed by your healthcare professional based upon review of your medical history. This starting dose of Follistim® AQ Cartridge to be injected with the Follistim Pen® under the skin is usually recommended for at least 7 days. Your healthcare professional may then adjust the dose based upon how your ovaries are responding to Follistim® AQ Cartridge. When an ultrasound examination shows that you are ready, another drug (hCG) may be injected to induce ovulation.

WHAT YOU WILL NEED FOR GIVING YOURSELF THE INJECTION

- Follistim Pen®, a Follistim® AQ Cartridge (follitropin beta injection), the BD Micro-Fine™ Pen Needle provided with the cartridge.
- Alcohol, cotton balls or alcohol pads/swabs, sterile gauze, antibacterial soap and a special safety container to discard the used needles, cartridges and/or other supplies.

IMPORTANT NOTICE

Please read all instructions for the use of the Follistim Pen® before administering the Follistim® AQ Cartridge.

- The Follistim Pen® is a precision injection device which is only to be used with the Follistim® AQ Cartridge. It is very important that you read and follow all directions for its use. As with all injection systems, failure to do so could result in an incorrect dose being given.
- Injecting cold drug is likely to cause discomfort. Therefore, it is recommended you allow the drug to reach room temperature before taking the injection. The needle should not be attached until just before the injection.

3. When injecting beneath the skin, always fully depress the Injection Button for a full 5 seconds. During these 5 seconds, leave the needle in the skin to ensure delivery of the full dose of Follistim[®] AQ Cartridge (follitropin beta injection).
4. Follistim Pen[®] is designed for use by one person only and should not be shared with others.
5. The BD Micro-Fine[™] Pen Needle is for use only with Follistim Pen[®]. Each BD Micro-Fine[™] Pen Needle is for one injection only.
6. Follistim Pen[®] is not recommended for the blind or visually impaired user without the assistance of an individual with good vision, trained in the proper use of the injection device.
7. Keep a record of every injection that has been taken from a Follistim[®] AQ Cartridge. A patient diary is available with the Instructions for Use Manual. This will allow you to calculate the daily amount of medication remaining in the cartridge by subtracting the injected amount from the 150 IU (orange), 300 IU (silver), 600 IU (gold) and/or 900 IU (blue) as indicated as the content on the cartridge label.
8. Your healthcare professional will decide on the dose of Follistim[®] AQ Cartridge to be given. This dose may be increased or decreased as your treatment progresses depending on your individual type of treatment. If you have previously used gonadotropins, your dose may be different with Follistim[®] AQ Cartridge. Again, your healthcare professional will decide the dose based upon your medical history.

INSTRUCTIONS FOR USE

BEFORE USING FOLLISTIM PEN[®] FOR THE FIRST TIME, READ THESE INSTRUCTIONS CAREFULLY. THEY ARE DIVIDED INTO SECTIONS. EACH SECTION HAS A NUMBER OF STEPS.

KEEP THIS LEAFLET IN A SAFE PLACE AND REFER TO IT WHEN QUESTIONS ARISE.

The main actions contained in this patient leaflet that must be learned are:

1. Loading the Follistim Pen[®]
2. Dialing the prescribed dose
3. Using the Follistim Pen[®] to give yourself an injection of Follistim[®] AQ Cartridge

The Follistim Pen[®] is a very precise injection device. It is easy to use and convenient. The special features allow you to inject Follistim[®] AQ Cartridge safely and effectively.

Follistim[®] AQ Cartridge using Follistim Pen[®] can be administered in prescribed doses from 50 International Units (IU) up to 450 IU, in marked 25 IU increments. The Dosage Scale on the Pen has easy-to-read numbers and audible clicks to help you set the correct dose. Incorrect settings are easily corrected without loss of drug.

- Follistim[®] AQ Cartridges and BD Micro-Fine[™] Pen Needles may only be used with Follistim Pen[®].
- Do not separate the three parts of the Follistim Pen[®], shown below, until told to do so in the instructions.

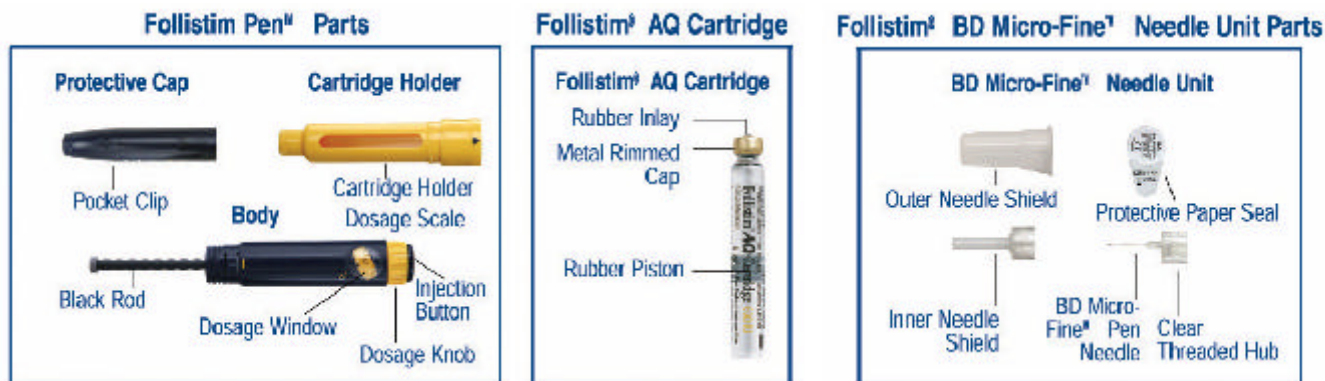
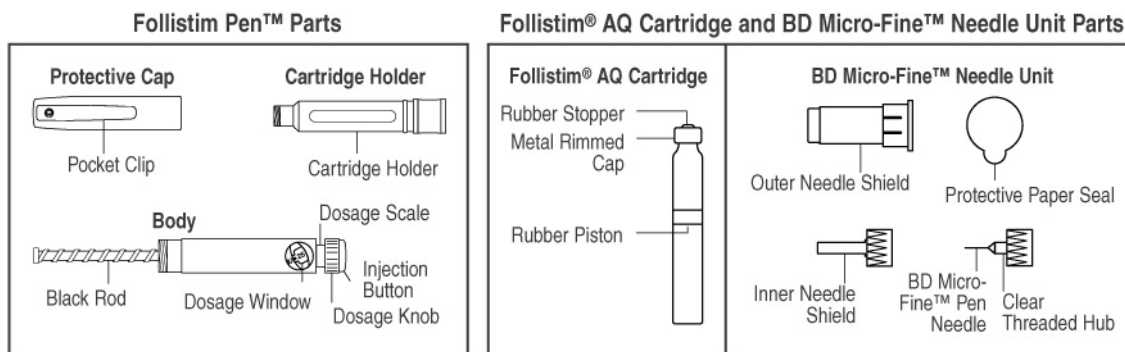
INJECTION INSTRUCTIONS FOR FOLLISTIM[®] AQ CARTRIDGE WITH THE FOLLISTIM PEN[®]

**Carefully read these instructions before injecting Follistim[®] AQ Cartridge with the Follistim Pen[®]
Do not use Follistim[®] AQ Cartridge with the Follistim Pen[®] unless your healthcare professional has**

taught you the right way to inject it and you understand everything. Ask your healthcare professional if you have any questions.



Figure shown not actual size

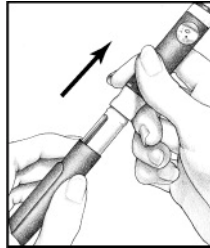


USING THE FOLLISTIM PEN®

Follow these steps:

- Before you use the Follistim Pen® for the first time
- When you replace the cartridge

Note: Always wash your hands thoroughly with antibacterial soap and water before you use the Follistim Pen® or when you replace the cartridge.

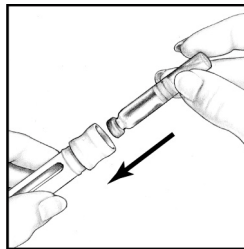


1. While holding the Pen Body firmly with one hand, pull off the Protective Cap with your other hand. Put the cap aside on a clean, dry surface.



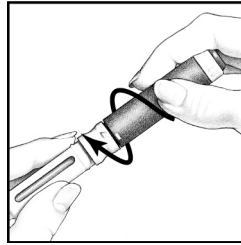
2. Unscrew the entire Pen Body from the Cartridge Holder. Place the Cartridge Holder and the Pen Body aside on a clean, dry surface.

LOADING THE FOLLISTIM PEN®



3. Take the correct size Follistim® AQ Cartridge (i.e., 150 IU, 300 IU, 600 IU or 900 IU) out of its package as prescribed by your healthcare professional. Do not use the Follistim® AQ Cartridge if the medicine contains particles or it is not clear. Make sure the medicine is at room temperature before using. Clean the Rubber Inlay on the cartridge with an alcohol pad. Pick up the Cartridge Holder and place the cartridge into the Cartridge Holder. Insert the Metal Rimmed Cap end first.

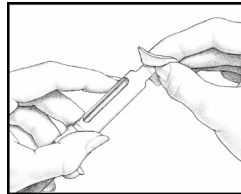
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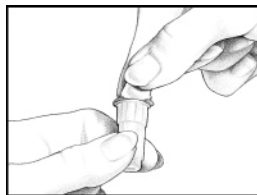
- 180 4. Pick up the Pen Body and lower it into the Cartridge Holder. The black rod must press against the
181 Rubber Piston on the cartridge. Screw the Pen Body fully onto the Cartridge Holder. Make sure there is
182 no gap between the Pen Body and the Cartridge Holder. The arrow (▲) on the Cartridge Holder
183 should point to the middle of the yellow alignment mark (■) on the blue Pen Body.

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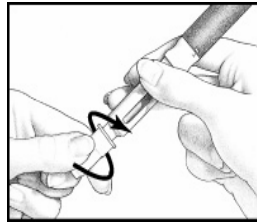
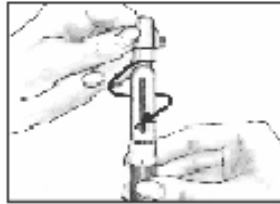
- 186 5. You must use a new BD Micro-Fine™ Pen Needle with each injection. Never reuse a needle. Attach a
187 BD Micro-Fine™ Pen Needle after you make sure there is a Follistim® AQ Cartridge in the Cartridge
188 Holder. Clean the open end of the Cartridge Holder with an alcohol pad.



189

- 190 6. Pick up your BD Micro-Fine™ Pen Needle that is in an Outer Needle Shield. Peel off the protective
191 paper seal. Do not touch the needle or place an open needle on any surface.

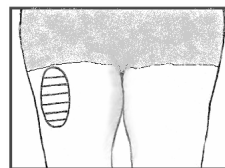
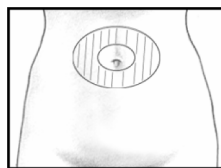
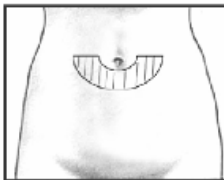
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- 194 7. Hold the Outer Needle Shield firmly in one hand while holding the Cartridge Holder firmly in the other
195 hand. Push the end of the Cartridge Holder into the Outer Needle Shield. Screw them tightly together.
196 Place your Follistim Pen® with the attached needle, flat on a clean, dry surface.

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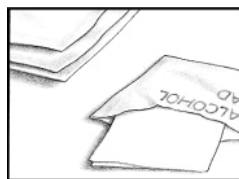
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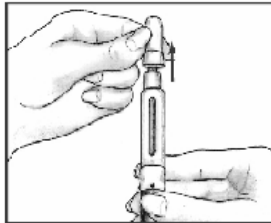
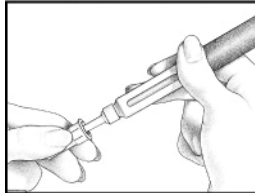
- 200 8. The best place for injection is in the abdomen, which is the stomach area below the belly button (navel)
201 or in the upper leg. Your healthcare professional can show you other places where you can inject
202 Follistim® AQ Cartridge. Change your injection site a little bit with each injection to lower your chances
203 for skin reactions.

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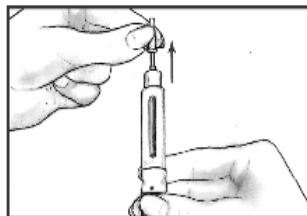
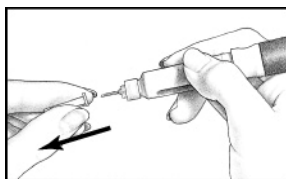
9. Use a swab moistened with alcohol to clean the skin area where the needle will enter to remove any surface bacteria. Clean about two inches around the injection site where the needle will be inserted. Let the alcohol dry on your skin for at least one minute before injecting the medicine.



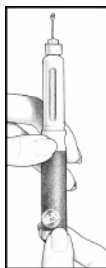
10. Pull the Outer Needle Shield gently, leaving the Inner Needle Shield in place (covering the needle, which is now attached to the Pen). ***Do not throw the Outer Needle Shield away.*** You will need it to dispose of the needle after injecting the medicine. Instructions for disposing the needle are given later in this leaflet.

Important:

- **Do not touch the needle or leave it uncapped without Inner Needle Shield so that it remains sterile.**
- **Use a new, sterile BD Micro-Fine™ Pen Needle for each injection. Only use the BD Micro-Fine™ 0.33 mm x 12.7 mm (29G) Pen needles as supplied with the Follistim® AQ Cartridge.**



11. Carefully remove the Inner Needle Shield and discard it. ***Do not touch the needle or let it touch any surface while uncapped.***



12. Hold the Follistim Pen® with the needle pointing upwards. Tap the Cartridge Holder gently with your finger to help air bubbles rise to the top of the needle. The small amount of air bubble will not affect the amount of medicine you receive.

If you have loaded a new, unused cartridge into the Follistim Pen®, always follow these steps:

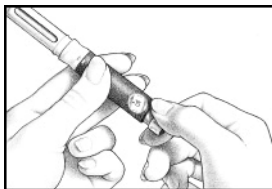
- a. Dial the Dosage Knob until you hear one click. With the needle pointing upwards, push in the Injection Button.
- b. Look for a droplet at the tip of the needle.
- c. If you still do not see a droplet, repeat Step a. (above) until you see droplet. You must make sure you see a droplet of medicine or you may not inject the correct amount of medicine.

If you have already used the Follistim® AQ Cartridge and you need to give yourself another dose, simply attach a new BD Micro-Fine™ Pen Needle and look for a droplet forming at the tip of the needle. If you see a droplet, go to step 13. If no droplet is seen, follow steps a, b and c above.

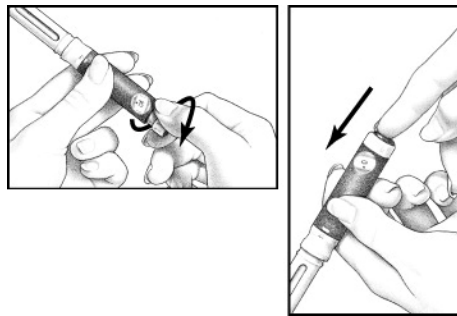
Important:

- Steps a, b and c need to be performed every time you load a new, unused cartridge in the Follistim Pen®.
- Always check the drug flow by following the directions in Step 12. This will ensure that the correct dose of Follistim® AQ Cartridge is injected. If you do not check drug flow, you could receive less drug than the dose that you dialed.

DIALING THE PRESCRIBED DOSE



13. Your Follistim[®] AQ Cartridge will contain one of the following color-coded cartridge sizes: 150 IU (orange), 300 IU (silver), 600 IU (gold) or 900 IU (blue). Record the Follistim[®] AQ Cartridge content in your Follistim Pen[®] Treatment Diary (refer to CHECKING THE DRUG LEVEL for more information). For doses of 50 IU up to 450 IU, turn the Dosage Knob until the dot beside the correct number on the Dosage Scale is sitting in the middle of the Dosage Window.



14. If by mistake you dial past the correct number, ***do not try to turn the Dosage Knob backward to fix the mistake.*** Continue to turn the Dosage Knob in the same direction past the 450 IU mark, as far as it will turn. The Dosage Scale must move freely. Push the Injection Button in all the way. Start to dial again starting from “0” upwards.

By following these directions, you will not lose any medicine from the Follistim[®] AQ Cartridge.

Important:

- If you turn the Dosage Knob backward to correct the mistake, it will not damage the Pen, but you will lose some medication from the Follistim[®] AQ Cartridge.
- Never dial your dose or try to correct a dialing mistake when the needle is still in your skin as this may result in your receiving an incorrect dose.
- If your prescribed dose exceeds the deliverable dose of Follistim Pen[®] or exceed the amount remaining in the cartridge, you will need to give yourself more than one injection.

**USING THE FOLLISTIM PEN[®] TO GIVE YOURSELF AN INJECTION
OF FOLLISTIM[®] AQ CARTRIDGE**

Once you have set the Follistim Pen[®] to the correct dose, you are ready for your injection.



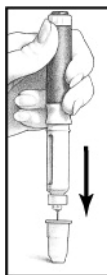
15. Pinch the already swabbed area of the skin between two fingers. With the other hand, insert the entire BD Micro-Fine™ Pen Needle straight into the skin. Press the injection button all the way in to make sure you give yourself a full injection. Wait for five seconds before pulling the needle out of the skin. The middle of the Dosage Window should display a dot next to the “0”. If the injection button does not push in all the way, and the number in the Dosage Window does not read “0”, it means there is not enough medication left in the cartridge to complete your prescribed dose. The number in the Dosage Window will give you the amount of medicine needed to complete your dose. Write this number down. This will be the number you dial for the completion of your dose. Start over with a new Follistim® AQ Cartridge and a new needle and follow all the instructions up to this step. Make sure you choose a different injection site to complete your dose of Follistim® AQ Cartridge.



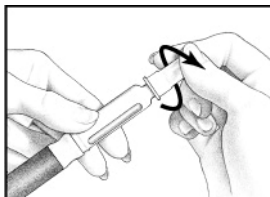
16. Pull out the BD Micro-Fine™ Needle and firmly press down on the injection site with an alcohol swab. Use the BD Micro-Fine™ Pen Needle for one injection only.

Important:

- If the dot next to the “0” is not in the middle of the Dosage Window and you cannot push the Injection Button all the way in, do not try to force down the button. Your Follistim® AQ Cartridge is probably empty. This means you have not received your full dose. Do not adjust the setting on the Dosage Scale. Follow the instructions for IF THERE IS NOT ENOUGH FOLLISTIM® AQ IN THE CARTRIDGE.



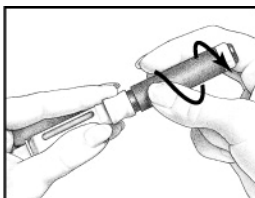
17. Place the Outer Needle Shield on a flat table surface with the opening pointing up. The opening of the Outer Needle Shield is the wider end with the rim. Without holding on to the Outer Needle Shield, carefully insert the needle (attached to the Follistim Pen®) into the opening of the Outer Needle Shield and push down firmly. The Outer Needle Shield should now be attached to the Cartridge Holder and cover the needle.



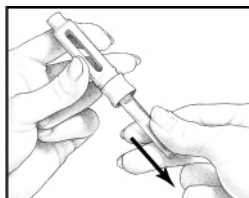
18. Grip the Outer Needle Shield and use it to unscrew the needle from the Cartridge Holder. Your healthcare professional can advise you on how to obtain a special container for proper needle disposal. Safely, dispose the Outer Needle Shield with the used needle right away. Do not throw away in a trash can. If there is Follistim® AQ Cartridge medicine left for more injections, put the Pen Cap back on the Pen Body and store your Follistim Pen® in a safe place in the refrigerator (**not in the freezer**) or at room temperature. ***Never store the Follistim Pen® with a needle attached to it.*** If you are giving an injection to another person, be very careful when removing the needle from the skin. Accidental needle sticks can transmit potentially serious or grave infectious diseases.

Important:

- Use the BD Micro-Fine™ Pen Needle for one injection only.
- Dispose of the used needle inside the Outer Needle Shield immediately in a properly secured container as instructed by your healthcare professional. Never leave needles where anyone can accidentally prick themselves.
- Always unscrew the needle by following the directions in Steps 17 and 18 before you put the Follistim Pen® away.
- Never store the Follistim Pen® with a needle attached to it. If you store the Follistim Pen® with the needle attached, the drug could leak out and there is risk of contamination.
- Never leave needles where others can pick them up.



19. Before you remove the empty Follistim® AQ Cartridge from the Follistim Pen®, unscrew the needle by following Steps 17 and 18. Unscrew the Pen Body from the Cartridge Holder.



20. Put the Pen Body down on a clean, dry surface and remove the empty Follistim[®] AQ Cartridge from the Cartridge Holder. Safely, dispose of the empty Follistim[®] AQ Cartridge right away in the same special container that you used for the needle disposal. Do not put the cartridge in a trash can.

Now, you may either:

- Put the Follistim Pen[®] back together without a Follistim[®] AQ Cartridge and store for your next injection
- OR**
- Insert a new Follistim[®] AQ Cartridge into the Cartridge Holder, put your Follistim Pen[®] back together, and store safely in the refrigerator or at room temperature.

CHECKING THE DRUG LEVEL

When you are advised on the number of prescribed doses which can be extracted from the full unused Follistim[®] AQ Cartridge (follitropin beta injection), then do not use the cartridge beyond the advised number of doses. Otherwise, you will run the risk that there will not be enough volume of drug for your prescribed dose.

Starting with the initial injection, you should begin using your Follistim Pen[®] Treatment Diary as follows:

- a. Record the Follistim[®] AQ Cartridge content. This will either be 150, 300, 600 or 900 IU depending on what your healthcare professional has prescribed for you.
- b. Record the daily dose you have been prescribed for your injection.
- c. Subtract your Day 1 dose from the Follistim[®] AQ Cartridge deliverable content (150, 300 or 600 or 900 IU) (see example below). This will give you the remaining Follistim[®] AQ Cartridge content.

After Day 1, continue to record your daily injections in your Treatment Diary as follows:

- d. Place the number recorded on Day 1 in the remaining Follistim[®] AQ Cartridge contents box in the Day 2 Follistim[®] AQ Cartridge content box.
- e. Subtract your Day 2 dose from the Follistim[®] AQ Cartridge content you just recorded in Step d. This will give you the remaining Follistim[®] AQ Cartridge content. Again, record this number in the correct box.

Date	Daily Dose to be Used (IUs/day)	Follistim [®] AQ Cartridge Content	Remaining Follistim [®] AQ Cartridge Content
mm/dd/yy	150	600	450
mm/dd/yy	150	450	300
mm/dd/yy	150	300	150

If there is any doubt that there is not enough drug in the Follistim® AQ Cartridge for your prescribed dose, see section ‘IF THERE IS NOT ENOUGH FOLLISTIM® AQ IN THE CARTRIDGE’.

IF THERE IS NOT ENOUGH FOLLISTIM® AQ IN THE CARTRIDGE

If you realize before you inject that you do not have enough drug remaining in your Follistim® AQ Cartridge for your complete dose, proceed to Step 1 (below).

OR

If you have already inserted the needle at the injection site and the Injection Button will not push in all the way, then there is not enough drug contained in the cartridge. The number in the Dosage Window will not read “0” – this means that there is not enough drug remaining in the Follistim® AQ Cartridge to complete your dose. In this case, proceed to Step 2 (below).

Important:

- **When there is not enough drug contained in the Follistim® AQ Cartridge to complete your injection, the Injection Button will not push in all the way and the number in the Dosage Window will not read “0”. If this occurs, proceed with the steps that follow.**

1. If you realize you do not have enough drug remaining in your Follistim® AQ Cartridge, you have 2 options:

Option #1: Remove the Follistim® AQ Cartridge as outlined in Steps 19 and 20. Insert a new cartridge into the Follistim Pen® (see Steps 3 and 4). Continue with Steps 5 – 18 for your injection.

Option #2: Dial your dose and inject the remaining content in the Follistim® AQ Cartridge. The Dosage Knob Injection Button will not push in all the way and the Dosage Window number will not read “0” but will read the number of units you will need to complete your prescribed dose. Remember to write down the number of units needed to complete your dose. Remove the needle and dispose of it properly as outlined in Steps 17 and 18. Using the Dosage Knob, reset the Dial Window to “0” by turning the Dosage Knob past the 450 IU mark as far as it will turn and push the Injection Button in all the way. Insert a new cartridge into the Follistim Pen® and attach a new BD Micro-Fine™ needle (see Steps 3 – 12). Dial to the number of units you have written down to complete your prescribed dose. Prepare a different injection site and inject the remaining drug to complete your dose (refer to USING THE FOLLISTIM PEN® TO GIVE YOURSELF AN INJECTION OF FOLLISTIM® AQ CARTRIDGE).

2. If you have already inserted the needle at the injection site, inject the remaining content in the Follistim® AQ Cartridge. The Injection Button will not push in all the way and the number in the Dosage Window will not read “0” but will read the number of units you will need to complete your prescribed dose. Wait 5 seconds before withdrawing the needle from your skin and gently apply pressure to the injection site with an alcohol pad. Dispose the used needle properly as outlined in Steps 17 and 18. Remember to write down the number of units needed to complete your dose. Using the Dosage Knob, reset the Dial Window to “0” by turning the Dosage Knob past the 450 IU mark as far as it will turn and push the Injection Button in all the way. Insert a new cartridge into the Follistim Pen® and attach a new BD Micro-Fine™ needle (see Steps 3 – 12). Dial to the number you have recorded to complete your prescribed dose. Prepare a different injection site and inject the remaining drug to complete your dose

(refer to USING THE FOLLISTIM PEN[®] TO GIVE YOURSELF AN INJECTION OF FOLLISTIM[®] AQ CARTRIDGE).

GENERAL INFORMATION ABOUT THE FOLLISTIM[®] AQ CARTRIDGE

Ingredients in Follistim[®] AQ Cartridge

Follistim[®] AQ Cartridge contains the active ingredient follitropin beta. Inactive ingredients in the cartridges include: sucrose, sodium citrate, polysorbate, benzyl alcohol, L-methionine, water for injection, hydrochloric acid and/or sodium hydroxide.

Caring for the Follistim Pen[®]

1. Clean all exposed surfaces of the Follistim Pen[™] with a clean, damp cloth such as a paper towel. Never wash it in water, detergent or strong medical cleaners.
2. Handle the Follistim Pen[®] carefully to avoid causing damage. You could damage the Follistim Pen[®] by dropping it or handling it roughly.
3. Keep the Follistim Pen[®] away from dust and dirt.
4. If the Follistim Pen[®] breaks or is damaged, do not try to fix it yourself. Contact your healthcare professional.
5. Do not share your Follistim Pen[®] with another person.

Storing the Follistim Pen[®]

1. Store refrigerated, 2–8°C (36–46°F) until dispensed. Do not freeze. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until the expiration date, whichever occurs first. Once the rubber inlay of the Follistim[®] AQ Cartridge has been pierced by a needle, the product may be stored only for a maximum of 28 days at 2–25°C (36–77°F).
For proper storage of unused Follistim[®] AQ Cartridges, please see the package insert enclosed with Follistim[®] AQ Cartridges.
2. Follistim Pen[®] with a Follistim[®] AQ Cartridge should be protected from light.
3. Do not use past the indicated expiration date on the Follistim[®] AQ Cartridge.
4. Keep the Follistim Pen[®], Follistim[®] AQ Cartridge, and any other components out of the sight and reach of children.
5. After your treatment is finished, store the Follistim Pen[®] injection device as instructed by your healthcare professional.

PRECAUTIONS

- Do not share your Follistim Pen[®] with another person.
- The Follistim Pen[®] is not recommended for the blind or visually impaired user without the assistance of an individual with good vision, trained in the proper use of the injection device.
- The Follistim Pen[®] is only indicated for use with a Follistim[®] AQ Cartridge when prescribed for subcutaneous injection.

Care while using the BD Micro-Fine™ Pen Needle

- Only attach the BD Micro-Fine™ Pen Needle when you are ready to inject. Always remove the needle from the Follistim Pen® immediately and dispose of it properly in its Outer Needle Shield after you complete your injection.
- The Pen Needle Unit is sterile. To avoid contaminating the needle after opening, do not place it on any surface or touch exposed parts.
- Before attempting to replace a Follistim® AQ Cartridge, be sure that a BD Micro-Fine™ Pen Needle is not attached to the Follistim Pen®.
- Never dial your dose or attempt to correct a dialing error with the needle in your skin, as this may result in an incorrect dose.
- Proper procedures should be used for the disposal of the used needles (fixed in the Outer Needle Shield), “empty” cartridges, and leftover medication. Consult your healthcare professional on the proper procedures for disposal.
- The Follistim Pen® is intended for self-injection of Follistim® AQ Cartridge. If you are giving an injection to another person, be very careful when removing the needle from the skin. Accidental needle sticks can transmit infectious diseases.

While this leaflet summarizes important information about Follistim® AQ Cartridge, it does not contain all of the possible precautions, side effects, warnings, contraindications, and interactions that may be associated with your drug treatments. Your healthcare professional should discuss your treatment and possible side effects with you. If you would like more information, talk to your doctor or other healthcare professional. You can ask your pharmacist or doctor for information about Follistim® AQ Cartridge that is written for healthcare professionals.

For questions on information contained in this leaflet, call

1-866-836-5633

www.follistim.com

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BD Micro-Fine™ is a trademark of Becton, Dickinson and Company

Rx only



Manufactured for Organon USA Inc.
West Orange, NJ 07052
by Vetter Pharma-Fertigung GmbH & Co. KG
Ravensburg, Germany
and packaged by Organon (Ireland) Ltd.
Swords, Co. Dublin, Ireland

One sterile prefilled cartridge contains 175 IU of follitropin beta to deliver 150 IU.

Inactive Ingredients: Benzyl alcohol 10 mg/mL, L-methionine 0.5 mg/mL, polysorbate 20 0.2 mg/mL, sodium citrate dihydrate 14.7 mg/mL, sucrose 50 mg/mL and water for injection. Hydrochloric acid and/or sodium hydroxide are used to adjust pH to 7.

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber inlay of the cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2–25°C (36–77°F).

Protect from light. Do not freeze.

Dosage: Read enclosed prescribing information.

For more information, call 1-866-836-5633 or visit www.follistim.com



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by Vetter Pharma-Fertigung GmbH & Co. KG,
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Follistim[®] AQ Cartridge 150 IU

(follitropin beta injection)

NDC 0052-0303-01

**1 Sterile Prefilled 1.5 mL Cartridge
containing 0.210 mL and
3 BD Micro-Fine™ Pen Needles**

Follistim[®] AQ Cartridge 150 IU

(follitropin beta injection)

**For use only with Follistim Pen[®],
available separately**

For Subcutaneous Use



Rx only



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5315471-01 9/04 09

Lot:

Exp:

Follistim[®] AQ Cartridge 150 IU
(follitropin beta injection)

Follistim[®] AQ Cartridge 150 IU
(follitropin beta injection)

One sterile prefilled cartridge contains 350 IU of follitropin beta to deliver 300 IU.

Inactive Ingredients: Benzyl alcohol 10 mg/mL, L-methionine 0.5 mg/mL, polysorbate 20 0.2 mg/mL, sodium citrate dihydrate 14.7 mg/mL, sucrose 50 mg/mL and water for injection. Hydrochloric acid and/or sodium hydroxide are used to adjust pH to 7.

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber inlay of the cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2–25°C (36–77°F).

Protect from light. Do not freeze.

Dosage: Read enclosed prescribing information.

For more information, call 1-866-836-5633 or visit www.follistim.com



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Follistim® AQ Cartridge 300 IU
(follitropin beta injection)

Follistim® AQ Cartridge 300 IU
(follitropin beta injection)

NDC 0052-0313-01

1 Sterile Prefilled 1.5 mL Cartridge
containing 0.420 mL and
6 BD Micro-Fine™ Pen Needles

Follistim® AQ Cartridge 300 IU
(follitropin beta injection)

For use only with Follistim Pen®,
available separately

For Subcutaneous Use



Rx only



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5315389-02 9/04 09

Lot:

Exp:

One sterile prefilled cartridge contains 650 IU of follitropin beta to deliver 600 IU.

Inactive Ingredients: Benzyl alcohol 10 mg/mL, L-methionine 0.5 mg/mL, polysorbate 20 0.2 mg/mL, sodium citrate dihydrate 14.7 mg/mL, sucrose 50 mg/mL and water for injection. Hydrochloric acid and/or sodium hydroxide are used to adjust pH to 7.

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber inlay of the cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2–25°C (36–77°F).

Protect from light. Do not freeze.

Dosage: Read enclosed prescribing information.

For more information, call 1-866-836-5633 or visit www.follistim.com



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Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

NDC 0052-0316-01

1 Sterile Prefilled 1.5 mL Cartridge
containing 0.780 mL and
6 BD Micro-Fine™ Pen Needles

Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

For use only with Follistim Pen®,
available separately

For Subcutaneous Use



Rx only



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5315390-02 9/04 08

Lot:

Exp:

Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

One sterile prefilled cartridge contains 975 IU of follitropin beta to deliver 900 IU.

Inactive Ingredients: Benzyl alcohol 10 mg/mL, L-methionine 0.5 mg/mL, polysorbate 20 0.2 mg/mL, sodium citrate dihydrate 14.7 mg/mL, sucrose 50 mg/mL and water for injection. Hydrochloric acid and/or sodium hydroxide are used to adjust pH to 7.

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber inlay of the cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2–25°C (36–77°F).

Protect from light. Do not freeze.

Dosage: Read enclosed prescribing information.

For more information, call 1-866-836-5633 or visit www.follistim.com



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Follistim® AQ Cartridge 900 IU
(follitropin beta injection)

NDC 0052-0326-01

1 Sterile Prefilled 1.5 mL Cartridge
containing **1.170 mL** and
9 BD Micro-Fine™ Pen Needles

Follistim® AQ Cartridge 900 IU
(follitropin beta injection)

For use only with Follistim Pen®,
available separately

For Subcutaneous Use



Rx only



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5315472-01 9/04 07

Lot:

Exp:

Follistim® AQ Cartridge 900 IU
(follitropin beta injection)

Follistim® AQ Cartridge 900 IU
(follitropin beta injection)

One sterile prefilled cartridge contains 350 IU of follitropin beta to deliver 300 IU.

Inactive Ingredients: Benzyl alcohol 10 mg/mL, L-methionine 0.5 mg/mL, polysorbate 20 0.2 mg/mL, sodium citrate dihydrate 14.7 mg/mL, sucrose 50 mg/mL and water for injection. Hydrochloric acid and/or sodium hydroxide are used to adjust pH to 7.

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber inlay of the cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2–25°C (36–77°F).

Protect from light. Do not freeze.

Dosage: Read enclosed prescribing information.

For more information, call 1-866-836-5633 or visit www.follistim.com



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Follistim® AQ Cartridge 300 IU
(follitropin beta injection)

Follistim® AQ Cartridge 300 IU
(follitropin beta injection)

NDC 0052-0313-81

1 Sterile Prefilled 1.5 mL Cartridge
containing 0.420 mL and
6 BD Micro-Fine™ Pen Needles

Professional Sample – Not For Sale

Follistim® AQ Cartridge 300 IU
(follitropin beta injection)

For use only with Follistim Pen®,
available separately

For Subcutaneous Use



Rx only



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5322206-02 10/04 14

Lot:

Exp:

Follistim® AQ Cartridge 300 IU
(follitropin beta injection)

One sterile prefilled cartridge contains 650 IU of follitropin beta to deliver 600 IU.

Inactive Ingredients: Benzyl alcohol 10 mg/mL, L-methionine 0.5 mg/mL, polysorbate 20 0.2 mg/mL, sodium citrate dihydrate 14.7 mg/mL, sucrose 50 mg/mL and water for injection. Hydrochloric acid and/or sodium hydroxide are used to adjust pH to 7.

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. Once the rubber inlay of the cartridge has been pierced by a needle, the product can only be stored for a maximum of 28 days at 2–25°C (36–77°F).

Protect from light. Do not freeze.

Dosage: Read enclosed prescribing information.

For more information, call 1-866-836-5633 or visit www.follistim.com



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Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

NDC 0052-0316-81

1 Sterile Prefilled 1.5 mL Cartridge
containing 0.780 mL and
6 BD Micro-Fine™ Pen Needles

Professional Sample – Not For Sale

Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

For use only with Follistim Pen®,
available separately

For Subcutaneous Use



Rx only



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5322304-02 10/04 08

Lot:

Exp:

Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

Follistim® AQ Cartridge 600 IU
(follitropin beta injection)

NDC 0052-0303-01

Sterile Prefilled Cartridge
containing 0.210 mL

Follistim[®] AQ Cartridge 150 IU
(follitropin beta injection) **Rx only**

For Subcutaneous Use

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. **Protect** from light. Do not freeze.

Mfg. for Organon USA Inc., W. Orange, NJ 07052

8/04 01

Lot:

Exp:

52719/240

NDC 0052-0313-01

Sterile Prefilled Cartridge
containing 0.420 mL

Follistim[®] AQ Cartridge 300 IU

(Follitropin beta injection)

Rx only

For Subcutaneous Use

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. **Protect** from light. Do not freeze.

Mfg. for Organon USA Inc., W. Orange, NJ 07052

8/04 06

Lot:

Exp:

52957/240

NDC 0052-0316-01

Sterile Prefilled Cartridge
containing 0.780 mL

Follistim[®] AQ Cartridge 600 IU

(follitropin beta injection)

Rx only

For Subcutaneous Use

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. **Protect** from light. Do not freeze.

Mfg. for Organon USA Inc., W. Orange, NJ 07052

8/04 05

Lot:

Exp:

52959/240

NDC 0052-0326-01

Sterile Prefilled Cartridge
containing 1.170 mL

Follistim[®] AQ Cartridge 900 IU
(folitropin beta injection) **Rx only**

For Subcutaneous Use

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. **Protect** from light. Do not freeze.

Mfg. for Organon USA Inc., W. Orange, NJ 07052

8/04 03

Lot:

Exp:

52721/240

NDC 0052-0313-81

Professional Sample — Not For Sale

Sterile Prefilled Cartridge
containing 0.420 mL

Follistim[®] AQ Cartridge 300 IU
(follitropin beta injection)

Rx only

For Subcutaneous Use

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. **Protect** from light. Do not freeze.

Mfg. for Organon USA Inc., W. Orange, NJ 07052

8/04 11

Lot:

Exp:

52958/240

NDC 0052-0316-81

Professional Sample — Not For Sale

Sterile Prefilled Cartridge
containing 0.780 mL

Follistim[®] AQ Cartridge 600 IU

(follicle-stimulating hormone injection)

Rx only

For Subcutaneous Use

Storage: Store refrigerated, 2–8°C (36–46°F) until dispensed. Upon dispensing, the product may be stored by the patient at 2–8°C (36–46°F) until the expiration date, or at 25°C (77°F) for 3 months or until expiration date, whichever occurs first. **Protect** from light. Do not freeze.

Mfg. for Organon USA Inc., W. Orange, NJ 07052

9/04 06

Lot:

Exp:

53009/240