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_s:$mg^{-1}cm^{-1}$) = 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 $AUC_{0-\infty}$ 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)

	$AUC_{0-\infty}$ (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)

$AUC_{0-\infty}$ 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, multicenter 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, Multicenter 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® and Follistim® AQ Cartridge 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 (follitropin beta injection) 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 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 (follitropin beta injection) 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 (follitropin beta injection) 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 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 injection 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 doses 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 (follitropin beta injection) 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 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, multicenter study in 43 clomiphene-resistant women with chronic anovulation (WHO group II) who were treated with Follistim® AQ Cartridge (follitropin beta injection) for induction of ovulation, a stepwise increasing dose regimen was included. The starting dose was 75 IU of Follistim® AQ Cartridge 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 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 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 inlay 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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