

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FOLLISTIM® AQ Cartridge safely and effectively. See full prescribing information for FOLLISTIM® AQ Cartridge.

FOLLISTIM® AQ Cartridge (follitropin beta injection) for subcutaneous use

Initial U.S. Approval: 1997

RECENT MAJOR CHANGES

Dosage and Administration

Recommended Dosing in Anovulatory Women Undergoing Ovulation Induction (2.2) 09/2019
Recommended Dosing in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle (2.3) 09/2019

Warnings and Precautions

Abnormal Ovarian Enlargement (5.1) 09/2019
Ovarian Hyperstimulation Syndrome (OHSS) (5.2) 09/2019
Pulmonary and Vascular Complications (5.3) 09/2019
Multi-fetal Gestation and Birth (5.5) 09/2019
Ectopic Pregnancy (5.7) 09/2019
Spontaneous Abortion (5.8) 09/2019
Ovarian and Other Reproductive System Neoplasms (5.9) 09/2019
Laboratory Tests (5.10) (removed) 09/2019

INDICATIONS AND USAGE

Follistim AQ Cartridge is a gonadotropin indicated:

In Women for:

- Induction of Ovulation and Pregnancy in Anovulatory Infertile Women in Whom the Cause of Infertility is Functional and Not Due to Primary Ovarian Failure (1.1)
- Pregnancy in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle (1.2)

In Men for:

- Induction of Spermatogenesis in Men with Primary and Secondary Hypogonadotropic Hypogonadism (HH) in Whom the Cause of Infertility is Not Due to Primary Testicular Failure (1.3)

DOSAGE AND ADMINISTRATION

See Dose Conversion Table 1 for Follistim AQ Cartridge with Pen Injector (2.1)

In Anovulatory Women Undergoing Ovulation Induction (2.2):

- Starting daily dose of 50 international units of Follistim AQ Cartridge is administered subcutaneously for at least the first 7 days. The dose is increased by 25 or 50 international units at weekly intervals until follicular growth indicate an adequate response.
 - When an acceptable pre-ovulatory state is achieved, final oocyte maturation is achieved with 5,000 to 10,000 international units of urinary human chorionic gonadotropin (hCG).
 - The woman and her partner should have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent.

In Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization or Intracytoplasmic Sperm Injection Cycle (2.3):

- Starting dose of 200 international units (actual cartridge doses) of Follistim AQ Cartridge is administered subcutaneously for at least the first 7 days of treatment. Subsequent doses can be adjusted down or up based upon ovarian response as determined by ultrasound evaluation of follicular growth. Dosage reduction in high responders can be considered from the 6th day of treatment onward according to individual response.
 - Final oocyte maturation is induced with a dose of 5,000-10,000 international units of urinary hCG.
 - Oocyte (egg) retrieval is performed 34 to 36 hours later.

Induction of Spermatogenesis in Men (2.4):

- Pretreatment with urinary hCG alone (1,500 international units twice weekly) is required. If serum testosterone levels have not normalized after 8 weeks of hCG treatment, the dose may be increased to 3,000 international units twice a week.
- After normalization of serum testosterone levels, administer 450 international units per week (225 international units twice weekly or 150 international units three times weekly) of Follistim AQ Cartridge subcutaneously with the same pre-treatment hCG dose used to normalize testosterone levels.

DOSAGE FORMS AND STRENGTHS

Injection: Follistim AQ Cartridge 175 IU per 0.210 mL (3)
Injection: Follistim AQ Cartridge 350 IU per 0.420 mL (3)
Injection: Follistim AQ Cartridge 650 IU per 0.780 mL (3)
Injection: Follistim AQ Cartridge 975 IU per 1.170 mL (3)

CONTRAINDICATIONS

Women and men who exhibit:

- Prior hypersensitivity to recombinant hFSH products (4)
- High levels of FSH indicating primary gonadal failure (4)
- Presence of uncontrolled non-gonadal endocrinopathies (4)
- Hypersensitivity reactions related to streptomycin or neomycin (4)
- Tumors of the ovary, breast, uterus, testis, hypothalamus or pituitary gland (4)

Women who exhibit:

- Pregnancy (4, 8.1)
- Heavy or irregular vaginal bleeding of undetermined origin (4)
- Ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS) (4)

WARNINGS AND PRECAUTIONS

Treatment with Follistim AQ may result in:

- Abnormal Ovarian Enlargement: Monitor ovarian response carefully. (5.1)
- Ovarian Hyperstimulation Syndrome (OHSS): Follow current clinical practice for reducing the risk of OHSS during IVF or ICSI. Adherence to recommended dose and treatment regimen and careful monitoring of ovarian response is important to reduce the risk. The OHSS risk increases with 18 or more follicles of 11 mm or more in diameter. If OHSS develops, standard management should be implemented. (5.2)
- Pulmonary and Vascular Complications: Before treatment with Follistim AQ Cartridge, weigh benefits versus risk in women with generally recognized risk factors for thromboembolic events. Pregnancy itself may increase this risk. (5.3)
- Ovarian Torsion: Diagnose and treat immediately. (5.4)
- Multi-fetal Gestation and Birth: Advise patients of the potential risks associated with multiple births. (5.5)
- Congenital Anomalies: Slightly higher incidence after IVF or ICSI than spontaneous conception that may be due to parental characteristics or multiple pregnancies. (5.6)
- Ectopic Pregnancy: Monitor for possible extrauterine pregnancy. (5.7)
- Spontaneous Abortion: Reported for all gonadotropin treatments, including Follistim AQ Cartridge. (5.8)
- Ovarian and Other Reproductive System Neoplasms: Reported for all gonadotropin treatments, including Follistim AQ Cartridge. Increased risk of these tumors in women undergoing infertility treatment has not been established. (5.9)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 2\%$) in women undergoing ovulation induction are ovarian hyperstimulation syndrome, ovarian cyst, abdominal discomfort, abdominal pain and lower abdominal pain. (6.1)

The most common adverse reactions ($\geq 2\%$) in women undergoing controlled ovarian stimulation as part of an IVF or ICSI cycle are pelvic discomfort, headache, ovarian hyperstimulation syndrome, pelvic pain, nausea and fatigue. (6.1)

The most common ($\geq 2\%$) adverse reactions in men undergoing induction of spermatogenesis are headache, acne, injection site

reaction, injection site pain, gynecomastia, rash and dermoid cyst. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----USE IN SPECIFIC POPULATIONS -----

Nursing Mothers: It is not known whether this drug is excreted in human milk. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2019

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Follistim® AQ (follitropin beta injection) Cartridge is indicated:

In Women for:

1.1 Induction of Ovulation and Pregnancy in Anovulatory Infertile Women in Whom the Cause of Infertility is Functional and Not Due to Primary Ovarian Failure

Prior to initiation of treatment with Follistim AQ Cartridge:

- Women should have a complete gynecologic and endocrinologic evaluation.
- Primary ovarian failure should be excluded.
- The possibility of pregnancy should be excluded.
- Tubal patency should be demonstrated.
- The fertility status of the male partner should be evaluated.

1.2 Pregnancy in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle

Prior to initiation of treatment with Follistim AQ Cartridge:

- Women should have a complete gynecologic and endocrinologic evaluation and diagnosis of cause of infertility.
- The possibility of pregnancy should be excluded.
- The fertility status of the male partner should be evaluated.

In Men for:

1.3 Induction of Spermatogenesis in Men with Primary and Secondary Hypogonadotropic Hypogonadism (HH) in Whom the Cause of Infertility is Not Due to Primary Testicular Failure

Prior to initiation of treatment with Follistim AQ Cartridge:

- Men should have a complete medical and endocrinologic evaluation.
- Hypogonadotropic hypogonadism should be confirmed and primary testicular failure should be excluded.
- Serum testosterone levels should be normalized with human chorionic gonadotropin (hCG) treatment.
- The fertility status of the female partner should be evaluated.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If the solution is not clear and colorless or has particles in it, the solution should not be used.
- Do not add any other medicines into the Follistim AQ Cartridge.
- Follistim AQ Cartridge with the pen injector device delivers on average an 18% higher amount of follitropin beta when compared to reconstituted Follistim delivered with a conventional syringe and needle. When administering Follistim AQ Cartridge, a lower starting dose and lower dose adjustments (as compared to reconstituted Follistim) should be considered. For that purpose the following Dose Conversion Table is provided:

**Table 1: Follistim AQ Cartridge Administered Subcutaneously With the Follistim Pen
Dose Conversion Table***

Lyophilized recombinant FSH dosing with 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.

2.2 Recommended Dosing in Anovulatory Women Undergoing Ovulation Induction

The dosing scheme is stepwise and is individualized for each woman [see *Clinical Studies* (14.1)].

- A starting daily dose of 50 international units of Follistim AQ Cartridge is administered [see *Dosage and Administration* (2.1)] subcutaneously daily for at least the first 7 days.
- Subsequent dosage adjustments are made at weekly intervals based upon ovarian response. If an increase in dose is indicated by the ovarian response, the increase should be made by 25 or 50 international units of Follistim AQ Cartridge at weekly intervals until follicular growth monitored by transvaginal ultrasound indicates an adequate ovarian response. The concurrent determination of serum estradiol levels may also be useful.

The following should be considered when planning the woman's individualized dose:

- Appropriate Follistim AQ Cartridge dose adjustment(s) should be used to prevent multiple follicular growth and cycle cancellation.
- The maximum, individualized, daily dose of Follistim AQ Cartridge is 250 international units.
- Treatment should continue until ultrasonic visualizations approximate the pre-ovulatory conditions based on follicular development.
- When pre-ovulatory conditions are reached, 5,000 to 10,000 international units of urinary hCG are used to induce final oocyte maturation and ovulation.

If the ovarian monitoring suggests an increased risk of OHSS on the last day of Follistim AQ Cartridge therapy, follow current clinical practice for reducing the risk of OHSS [see *Warnings and Precautions* (5.1, 5.2)].

- The woman and her partner should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent.
 - During treatment with Follistim AQ Cartridge and during a two-week post-treatment period, the woman should be assessed at least every other day for signs of excessive ovarian stimulation.
- It is recommended that Follistim AQ Cartridge administration be stopped if the ovarian monitoring suggests an increased risk of OHSS or abdominal pain occurs. Most OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days post-ovulation. Follow current clinical practice for reducing the risk of OHSS [see *Warnings and Precautions* (5.1, 5.2)].

2.3 Recommended Dosing in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle

The dosing scheme follows a stepwise approach and is individualized for each woman.

- A starting dose of 200 international units (actual cartridge doses) of Follistim AQ Cartridge is administered [see *Dosage and Administration* (2.1)] subcutaneously daily for at least the first 7 days of treatment.
- Subsequent to the first 7 days of treatment, the dose can be adjusted down or up based upon the woman's ovarian response as determined by ultrasound evaluation of follicular growth. The concurrent determination of serum estradiol levels may also be useful. Dosage reduction in high responders can be considered from the 6th day of treatment onward according to individual response.

The following should be considered when planning the woman's individualized dose:

- For most normal responding women, the daily starting dose can be continued until pre-ovulatory conditions are achieved (seven to twelve days).
- For low or poor responding women, the daily dose should be increased according to the ovarian response. The maximum, individualized, daily dose of Follistim AQ Cartridge is 500 international units.
- For high responding women [those at particular risk of abnormal ovarian enlargement and/or ovarian hyperstimulation syndrome (OHSS)], decrease or temporarily stop the daily dose, or discontinue the cycle according to individual response. Follow current clinical practice for reducing the risk of OHSS. [See *Warnings and Precautions* (5.1, 5.2).]
- When a sufficient number of follicles of adequate size are present, dosing of Follistim AQ Cartridge is stopped and final maturation of the oocytes is induced by administering urinary hCG at a dose of 5,000 to 10,000 international units. If the ovarian monitoring suggests an increased risk of OHSS on the last day of Follistim AQ Cartridge therapy, follow current clinical practice for reducing the risk of OHSS [see *Warnings and Precautions* (5.1, 5.2)].
- Oocyte (egg) retrieval should be performed 34 to 36 hours following the administration of hCG.

2.4 Recommended Dosing for Induction of Spermatogenesis in Men

- Pretreatment with hCG is required prior to concomitant therapy with Follistim AQ Cartridge and hCG. An initial dosage of 1,500 international units of urinary hCG should be administered at twice weekly intervals to normalize serum testosterone levels. If serum testosterone levels have not normalized after 8 weeks of hCG treatment, the urinary hCG dose can be increased to 3,000 international units twice weekly [see *Clinical Studies* (14.3)].
- After normal serum testosterone levels have been reached, Follistim AQ Cartridge should be administered by subcutaneous injection concomitantly with hCG treatment. Follistim is given at a dosage of 450 international units per week, as either 225 international units twice weekly or 150 international units three times per week, in combination with the same hCG dose used to normalize testosterone levels. Based on delivery of a higher dose of follitropin beta with the Follistim AQ Cartridge and pen injector [see *Dosage and Administration* (2.1)], a lower dose of Follistim AQ Cartridge may be considered.

The concomitant therapy should be continued for at least 3 to 4 months before any improvement in spermatogenesis can be expected. If a man has not responded after this period, the combination therapy may be continued. Treatment response has been noted at up to 12 months.

3 DOSAGE FORMS AND STRENGTHS

Injection: Follistim AQ Cartridge 175 international units per 0.210 mL

Injection: Follistim AQ Cartridge 350 international units per 0.420 mL

Injection: Follistim AQ Cartridge 650 international units per 0.780 mL

Injection: Follistim AQ Cartridge 975 international units per 1.170 mL

4 CONTRAINDICATIONS

Follistim AQ Cartridge is contraindicated in women and men who exhibit:

- Prior hypersensitivity to recombinant hFSH products
- High levels of FSH indicating primary gonadal failure
- Presence of uncontrolled non-gonadal endocrinopathies (e.g., thyroid, adrenal, or pituitary disorders) [see *Indications and Usage* (1.1, 1.2, 1.3)]
- Hypersensitivity reactions to streptomycin or neomycin. Follistim AQ may contain traces of these antibiotics
- Tumors of the ovary, breast, uterus, testis, hypothalamus or pituitary gland

Follistim AQ Cartridge is also contraindicated in women who exhibit:

- Pregnancy [see *Use in Specific Populations* (8.1)]
- Heavy or irregular vaginal bleeding of undetermined origin
- Ovarian cysts or enlargement not due to polycystic ovary syndrome (PCOS)

5 WARNINGS AND PRECAUTIONS

Follistim AQ Cartridge should be used only by physicians who are experienced in infertility treatment. Follistim AQ Cartridge contains a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) [see *Warnings and Precautions* (5.2)] with or without pulmonary or vascular complications [see *Warnings and Precautions* (5.3)] and multiple births [see *Warnings and Precautions* (5.5)]. Gonadotropin therapy requires the availability of appropriate monitoring facilities.

Careful attention should be given to the diagnosis of infertility and in the selection of candidates for Follistim AQ Cartridge therapy [see *Indications and Usage* (1.1, 1.2, 1.3) and *Dosage and Administration* (2.2, 2.3, 2.4)].

Switching to Follistim AQ Cartridge from other brands (manufacturer), types (recombinant, urinary), and/or methods of administration (Follistim Pen, conventional syringe) may necessitate an adjustment of the dose [see *Dosage and Administration* (2)].

5.1 Abnormal Ovarian Enlargement

In order to reduce the risks associated with abnormal ovarian enlargement that may occur with Follistim AQ therapy, treatment should be individualized and the lowest effective dose should be used [see *Dosage and Administration* (2.2, 2.3)].

Careful monitoring, including use of ultrasound monitoring of ovarian response, is important to reduce the risk of overstimulation. The concurrent determination of serum estradiol levels may also be useful. [See *Warnings and Precautions* (5.2)].

If the ovaries are abnormally enlarged on the last day of Follistim AQ therapy, follow current clinical practice for reducing the risk of OHSS [see *Warnings and Precautions* (5.2)].

5.2 Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical entity distinct from uncomplicated ovarian enlargement. Clinical signs and symptoms of mild and moderate OHSS are abdominal pain, nausea, diarrhea, mild to moderate enlargement of ovaries and ovarian cysts. Severe OHSS may be life-threatening. Clinical signs and symptoms of severe OHSS are large ovarian cysts, acute abdominal pain, ascites, pleural effusion, hydrothorax, dyspnea, oliguria, hematological abnormalities and weight gain. In rare instances, venous or arterial thromboembolism may occur in association with OHSS [see *Warnings and Precautions* (5.3)]. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy have also been reported in association with OHSS.

OHSS may be caused by administration of human Chorionic Gonadotropin (hCG) and by pregnancy (endogenous hCG). Early OHSS usually occurs within 10 days after hCG administration and may be associated with an excessive ovarian response to gonadotropin stimulation. Late OHSS occurs more than 10 days after hCG administration, as a consequence of the hormonal changes with pregnancy. Because of the risk of developing OHSS, patients should be monitored for at least two weeks after hCG administration.

Women with known risk factors for a high ovarian response may be especially prone to the development of OHSS during or following treatment with Follistim AQ Cartridge. For women having their first cycle of ovarian stimulation, for whom risk factors are only partially known, close observation for early signs and symptoms of OHSS is recommended.

Follow current clinical practice for reducing the risk of OHSS during IVF or ICSI. Adherence to the recommended Follistim AQ Cartridge dose and treatment regimen and careful monitoring of ovarian response is important to reduce the risk of OHSS. To monitor the risk of OHSS, ultrasound assessments of follicular development should be performed prior to treatment and at regular intervals during treatment; the concurrent determination of serum estradiol levels may also be useful. In IVF or ICSI there is an increased risk of OHSS with 18 or more follicles of 11 mm or more in diameter.

If OHSS develops, standard and appropriate management of OHSS should be implemented and followed.

During clinical trials with Follistim or Follistim AQ Cartridge therapy, OHSS occurred in 7.6% of 105 women (OI) and 6.4% of 751 women (IVF or ICSI) treated with Follistim and Follistim AQ Cartridge, respectively.

5.3 Pulmonary and Vascular Complications

Serious pulmonary conditions, including acute respiratory distress syndrome, have been reported in women treated with gonadotropins.

Thromboembolic events, both in association with and separate from OHSS, have been reported following therapy with gonadotropins, including Follistim AQ Cartridge. Intravascular thrombosis, which may originate in venous or arterial vessels, can result in reduced blood flow to vital organs or the extremities. In women with generally recognized risk factors for thromboembolic events, such as a personal or family history, severe obesity, or thrombophilia, may have an increased risk of venous or arterial thromboembolic events, during or following treatment with gonadotropins, including Follistim AQ Cartridge. Sequelae of such reactions have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb and rarely in myocardial infarction. In rare cases, pulmonary complications and/or thromboembolic reactions have resulted in death. In women with recognized risk factors, the benefits of ovulation induction, in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment need to be weighed against the risks. It should be noted that pregnancy itself also carries an increased risk of thrombosis.

5.4 Ovarian Torsion

Ovarian torsion has been reported after treatment with gonadotropins including Follistim AQ Cartridge. Ovarian torsion may be related to OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cysts and polycystic ovaries. Damage to the ovary due to reduced blood supply can be limited by early diagnosis and immediate detorsion.

5.5 Multi-fetal Gestation and Birth

Multi-fetal gestation and births have been reported with all gonadotropin treatments including Follistim AQ Cartridge treatment. The woman and her partner should be advised of the potential risks for the mother (pregnancy and delivery complications) and the neonate (low birth weight) before starting treatment. For anovulatory women undergoing ovulation induction, monitoring follicular development with transvaginal ultrasonography may aid in determining whether or not to continue the cycle in order to reduce the risk of multi-fetal gestations. The concurrent determination of serum estradiol levels may also be useful. In women undergoing IVF or ICSI procedures, the risk of multiple pregnancy is mainly related to the number of embryos transferred.

5.6 Congenital Anomalies

The incidence of congenital malformations after IVF or ICSI 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 multi-fetal gestations after IVF or ICSI. There are no indications that the use of gonadotropins during IVF or ICSI is associated with an increased risk of congenital malformations.

5.7 Ectopic Pregnancy

Infertile women undergoing IVF or ICSI have an increased incidence of ectopic pregnancies. Early confirmation of an intrauterine pregnancy should be determined by transvaginal ultrasound.

5.8 Spontaneous Abortion

Spontaneous abortions (miscarriage) have been reported for all gonadotropin products, including Follistim AQ Cartridge. However, causality has not been established, but may be related to a number of factors, including the underlying infertility.

5.9 Ovarian and Other Reproductive System Neoplasms

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

5.10 Follistim Pen

The Follistim Pen is intended only for use with Follistim AQ Cartridge. The Follistim Pen is not recommended for the blind or visually impaired without the assistance of an individual with good vision who is trained in the proper use of the injection device.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Abnormal Ovarian Enlargement [see Warnings and Precautions (5.1)]
- Ovarian Hyperstimulation Syndrome [see Warnings and Precautions (5.2)]
- Pulmonary and Vascular Complications [see Warnings and Precautions (5.3)]
- Ovarian Torsion [see Warnings and Precautions (5.4)]
- Multi-fetal Gestation and Birth [see Warnings and Precautions (5.5)]
- Congenital Anomalies [see Warnings and Precautions (5.6)]
- Ectopic Pregnancy [see Warnings and Precautions (5.7)]
- Spontaneous Abortion [see Warnings and Precautions (5.8)]
- Ovarian and Other Reproductive System Neoplasms [see Warnings and Precautions (5.9)]

6.1 Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trial of another drug and may not reflect the rates observed in practice.

Ovulation Induction

In a single cycle, multi-center, assessor-blind, parallel group, comparative study, a total of 172 chronic anovulatory women who had failed to ovulate and/or conceive with clomiphene citrate therapy, were randomized and treated with Follistim (105) or a urofollitropin comparator. Adverse reactions with an incidence of greater than 2% in either treatment group are listed in Table 2.

Table 2: Common Adverse Reactions Reported at a Frequency of $\geq 2\%$ in an Assessor-Blind, Comparative Study of Anovulatory Women Receiving Ovulation Induction

System Organ Class/Adverse Reactions	Treatment Number (%) of Women	
	Follistim N=105 n (%)	Comparator N=67 n (%)
Gastrointestinal disorders		
Abdominal discomfort	3 (2.9)	1 (1.5)
Abdominal pain	3 (2.9)	2 (3.0)
Abdominal pain lower	3 (2.9)	1 (1.5)
Reproductive system and breast disorders		
Ovarian cyst	3 (2.9)	2 (3.0)
Ovarian hyperstimulation syndrome	8 (7.6)	3 (4.5)
General disorders and administration site conditions		
Pyrexia	0 (0.0)	2 (3.0)

Adverse reactions reported commonly (greater than or equal to 2% of women treated with Follistim) in other ovulation induction clinical trials were headache, abdominal distension, constipation, diarrhea, nausea, pelvic pain, uterine enlargement, vaginal hemorrhage and injection site reaction.

In Vitro Fertilization/Intracytoplasmic Sperm Injection

In a single cycle, multi-center, double-blind, parallel group, comparative study, a total of 1509 women were randomized to receive controlled ovarian stimulation with either Follistim AQ Cartridge (751 women were treated with Follistim AQ Cartridge) or a comparator and pituitary suppression with a gonadotropin releasing hormone (GnRH) antagonist as part of an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle. Table 3 lists adverse reactions with an incidence of greater than 2% in the group of women treated with Follistim AQ Cartridge.

Table 3: Common Adverse Reactions Reported at a Frequency of $\geq 2\%$ in a Randomized, Double-blind, Active-controlled, Comparative Study of Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization or Intracytoplasmic Sperm Injection Cycle

System Organ Class/Adverse Reactions	Follistim AQ Cartridge Treatment N = 751 n ^a (%)
Nervous System disorders	
Headache	55 (7.3%)
Gastrointestinal disorders	
Nausea	29 (3.9%)
Reproductive system and breast disorders	
Ovarian Hyperstimulation Syndrome	48 (6.4%)
Pelvic discomfort	62 (8.3%)
Pelvic Pain	41 (5.5%)
General disorders and Administration site conditions	
Fatigue	17 (2.3%)

^a n = number of women with the adverse reaction

Induction of Spermatogenesis

In an open-label, non-comparative clinical trial, 49 men with hypogonadotropic hypogonadism were enrolled to receive pretreatment with hCG, followed by combination therapy with hCG and Follistim for induction of spermatogenesis. Of the 49 men, 30 received weekly Follistim doses of 450 international units; 24 of these 30 men received a total of 48 weeks of treatment with Follistim. Adverse reactions occurring with an incidence of greater than 2% in the 30 men treated with Follistim are listed in Table 4.

Table 4: Common Adverse Reactions Reported at a Frequency of $\geq 2\%$ in an Open-Label Clinical Trial in Men with Hypogonadotropic Hypogonadism

System Organ Class/Adverse Reactions	Follistim Treatment N=30 n (%)
Nervous system disorders	
Headache	2 (6.7)
General disorders and administration site disorders	
Injection site reaction	2 (6.7)
Injection site pain	2 (6.7)
Skin and cutaneous tissue disorders	
Acne	2 (6.7)
Rash	1 (3.3)
Reproductive system and breast disorders	
Gynecomastia	1 (3.3)
Neoplasms benign, malignant and unspecified	
Dermoid cyst	1 (3.3)

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of Follistim and/or Follistim AQ Cartridge. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders

Abdominal distension, abdominal pain, constipation, diarrhea

General disorders and administration site conditions

Injection site reaction

Reproductive system and breast disorders

Breast tenderness, metrorrhagia, ovarian enlargement, vaginal hemorrhage

Skin and subcutaneous tissue disorders

Rash

Vascular disorders

Thromboembolism [see Warnings and Precautions (5.3)]

7 DRUG INTERACTIONS

No drug-drug interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X: Follistim AQ Cartridge should not be used during pregnancy [see Contraindications (4)].

8.3 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, 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.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

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

10 OVERDOSAGE

Aside from the possibility of Ovarian Hyperstimulation Syndrome [see Warnings and Precautions (5.2, 5.3)] and multiple gestations [see Warnings and Precautions (5.5)], there is no additional information concerning the consequences of acute overdosage with Follistim AQ Cartridge.

11 DESCRIPTION

Follistim AQ Cartridge 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 [as determined by the Ph. Eur. test for FSH *in vivo* bioactivity and on the basis of the molar extinction coefficient at 277 nm ($\epsilon_{277} = 1.066$).

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 international unit per 40,000 international units FSH. The compound is considered to contain no LH activity.

The amino acid sequence and tertiary structure of the product are indistinguishable from that of hFSH of urinary source. Also, based on available data derived from physico-chemical 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 WHO International Standard for Follicle Stimulating Hormone (FSH) Recombinant, Human for Bioassay (code 92/642), issued by the World Health Organization Expert Committee on Biological Standardization (1995). Under current storage conditions, Follistim AQ may contain up to 11% of oxidized follitropin beta.

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Women:

Follicle-stimulating hormone (FSH), the active component in Follistim AQ Cartridge, 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.

Men:

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

12.3 Pharmacokinetics

Pharmacokinetic parameters for Follistim AQ Cartridge were evaluated in an open-label, single-center, randomized study in 20 healthy women. Serum FSH values from a single subcutaneous injection of reconstituted Follistim lyophilized powder administered by conventional syringe were compared to those values following a single subcutaneous injection of Follistim AQ Cartridge administered with the Follistim Pen injector. Administration of follitropin beta with the Follistim Pen resulted in an 18% increase in $AUC_{0-\infty}$ and C_{max} . The 18% difference in serum FSH concentrations resulting from administration of 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 5: 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:

Women:

The bioavailability of Follistim following subcutaneous and intramuscular administration was investigated in healthy, pituitary-suppressed women given a single 300 international units dose. In these women, the area under the curve (AUC), expressed as the mean \pm SD, was equivalent between the subcutaneous (455.6 ± 141.4 IU*h/L) and intramuscular (445.7 ± 135.7 IU*h/L) routes of administration. However, equivalence could not be established with respect to the peak serum FSH levels (C_{max}). The C_{max} achieved after subcutaneous administration and intramuscular administration was 5.41 ± 0.72 international units/L and 6.86 ± 2.90 international units/L, respectively. After subcutaneous or intramuscular injection the apparent dose absorbed was 77.8% and 76.4%, respectively.

The pharmacokinetics and pharmacodynamics of a single, intramuscular dose (300 international units) of Follistim were also investigated in a group (n=8) of gonadotropin-deficient, but otherwise healthy women. In these women, FSH (mean \pm SD) AUC was 339 ± 105 international units*h/L, C_{max} was 4.3 ± 1.7 international units/L. C_{max} occurred at approximately 27 ± 5.4 hours after intramuscular administration.

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

Men:

No PK studies were conducted using Follistim AQ Cartridge in men. Exposures of follitropin beta from Follistim AQ Cartridge and Follistim are expected to be equivalent after adjusting for the 18% difference in dose [see *Dosage and Administration* (2)].

Serum levels of FSH were measured in a clinical study that compared the effects of two different dosing schedules of Follistim (150 international units three times a week or 225 international units twice a week) administered by subcutaneous injection concurrently with chorionic gonadotropin for induction of spermatogenesis in hypogonadotropic hypogonadal men. Administration of Follistim was started at Week 17. Mean serum trough concentrations of FSH remained fairly constant over the treatment period. At the end of treatment (Week 64), the mean serum trough concentrations of FSH were 2.09 international units/L in the 150 international units group and 3.22 international units/L in the 225 international units group. Serum trough concentrations of FSH measured prior to the first Follistim injection on the Mondays of active treatment period (Weeks 17 to 64) and one week after the end of treatment period are presented in Figure 1.

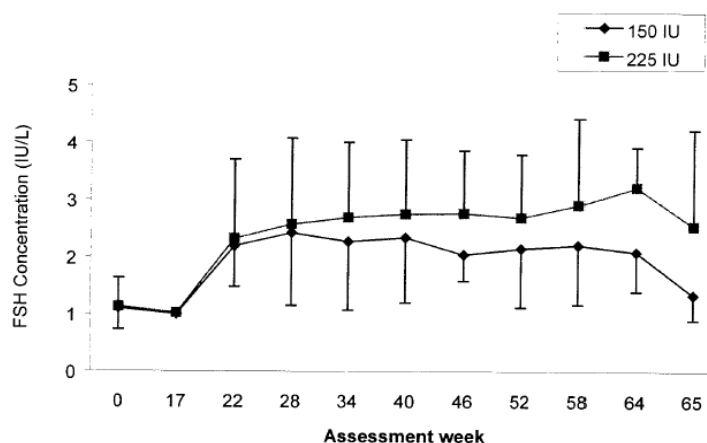


Figure 1: Mean (SD) Serum Trough Concentrations of FSH in Men Following Subcutaneous Administration of Follistim Using Two Different Dosing Schedules (150 International Units Three Times a Week or 225 International Units Twice a Week)

Distribution:

The volume of distribution of Follistim in healthy, pituitary-suppressed, women following intravenous administration of a 300 international units dose was approximately 8 L.

Metabolism:

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

Elimination:

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

Use in Specific Populations:

Body weight: The effect of body weight on the pharmacokinetics of Follistim was evaluated in a group of European and Japanese women who were significantly different in terms of body weight. The European women had a body weight of (mean \pm SD) 67.4 ± 13.5 kg and the Japanese subjects were 46.8 ± 11.6 kg. Following a single intramuscular dose of 300 international units of Follistim, the AUC was significantly smaller in European women (339 ± 105 international units*h/L) than in Japanese women (544 ± 201 international units*h/L). However, clearance per kg of body weight was essentially the same for the respective groups (0.014 and 0.013 L/hr/kg).

Geriatric Use: The pharmacokinetics of Follistim has not been studied in geriatric subjects.

Pediatric Use: The pharmacokinetics of Follistim has not been studied in pediatric subjects.

Renal Impairment: The effect of renal impairment on the pharmacokinetics of Follistim has not been studied.

Hepatic Impairment: The effect of hepatic impairment on the pharmacokinetics of Follistim has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

14 CLINICAL STUDIES

14.1 Ovulation Induction

The efficacy of Follistim for ovulation induction was evaluated in a randomized, assessor-blind, parallel-group comparative, multicenter safety and efficacy study of 172 chronic anovulatory women (105 subjects on Follistim) who had previously failed to ovulate and/or conceive during clomiphene citrate treatment. The study results for ovulation rates are summarized in Table 6 and those for pregnancy rates are summarized in Table 7.

Table 6: Cumulative Ovulation Rates

Cycle	Follistim (n=105)
First treatment cycle	72%
Second treatment cycle	82%
Third treatment cycle	85%

Table 7: Cumulative Ongoing^{*†} Pregnancy Rates

Cycle	Follistim (n=105)
First treatment cycle	14%
Second treatment cycle	19%
Third treatment cycle	23%

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

† Study was not powered to demonstrate this outcome.

14.2 Controlled Ovarian Stimulation as Part of an In Vitro Fertilization (IVF) or Intracytoplasmic Sperm Injection (ICSI) Cycle

The efficacy of Follistim AQ Cartridge was evaluated in a randomized, double-blind, active-controlled study of 1,509 healthy normal ovulatory women (mean age, body weight, and body mass index of 32 years, 68 kg and 25 kg/m², respectively) treated for one cycle with controlled ovarian stimulation and pituitary suppression with a GnRH antagonist as part of an in vitro fertilization or intracytoplasmic sperm injection cycle. This 2008 study was conducted in Europe and North America (United States and Canada). Approximately 54% of the subjects were from North America. The overall results, as well as the results from North America only, for clinical pregnancy are summarized in Table 8.

Table 8: Pregnancy Results from Treatment With Follistim AQ Cartridge and a GnRH Antagonist in Normal Ovulatory Women Undergoing Controlled Ovarian Stimulation as Part of an In Vitro Fertilization or Intracytoplasmic Sperm Injection Cycle.* Intent-to-Treat Population (ITT)

Parameter	Follistim AQ Cartridge Overall data (n=750)	Follistim AQ Cartridge North American data (n=403)
Clinical pregnancy rate/cycle initiation [†]	41.1%	48.9%

* Single treatment cycle results

† Clinical pregnancy was assessed ≥6 weeks after transfer of one or two embryos.

14.3 Induction of Spermatogenesis

The safety and efficacy of Follistim administered by subcutaneous injection concomitantly with chorionic gonadotropin for injection (hCG) has been examined in a multicenter, open-label, non-comparator clinical study for induction of spermatogenesis in hypogonadotropic hypogonadal men. The study compared the effects of two different Follistim dosing schedules on semen parameters and serum levels of follicle stimulating hormone (FSH). The multicenter study involved a 16-week pretreatment phase with urinary hCG at a dosage of 1,500 international units twice a week to normalize serum testosterone levels. If serum testosterone levels did not normalize after 8 weeks of hCG treatment, the urinary hCG dose could have been increased to 3,000 international units twice a week. This phase was followed by a 48-week treatment phase. Men who were still azoospermic after the pretreatment phase were randomized to receive either 225 international units Follistim together with 1,500 international units urinary hCG twice a week or 150 international units Follistim three times a week together with 1,500 international units urinary hCG twice weekly. Men who required 3,000 international units of urinary hCG twice a week in the pretreatment phase were continued on that dosage during the treatment phase. The mean age of patients in both treatment groups was approximately 30 years (range 18 to 47 years). At baseline, mean left and right testis volumes were 4.61 ± 2.94 mL and 4.57 ± 3.00 mL, respectively, in the group receiving three weekly injections of Follistim. For the group receiving two weekly injections of Follistim, the mean left and right testis volumes were 6.54 ± 2.45 mL and 7.21 ± 2.94 mL, respectively, at baseline. The primary efficacy endpoint was the percentage of patients with a mean sperm density of ≥1 × 10⁶/mL on their last two treatment assessments. The outcomes of treatment in the 30 men enrolled in the treatment phase are summarized in Table 9.

Table 9: Number of Men Receiving Follistim Who Achieved a Mean Sperm Density of $\geq 10^6$ /mL on Their Last Two Treatment Assessments

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

Overall, the median time to reach a sperm concentration of 10^6 per mL was 165 days (range 25 to 327 days) in patients who demonstrated a sperm concentration of at least 10^6 per mL. The median time to reach a sperm concentration of at least 10^6 per mL was 186 days (range 25 to 327 days) for the 150 international units group and 141 days (range 43 to 204 days) for the 225 international units group. No pregnancy data were collected during the trial.

The local tolerance data were comparable between the two treatment groups. The mean percentage of days without pain calculated for all subjects in the treatment period was 91.3% for patients in the 150 international units (three times a week) and 76.0% for patients in the 225 international units (two times a week) Follistim treatment groups. In the 225 international units (twice per week) group, local symptoms judged as severe by the investigator were: itching in 1 patient (7%), pain in 2 patients (13%), bruising in 2 patients (13%), swelling in 2 patients (13%), and redness in 1 patient (7%). In the 150 international units (three times per week) group, 1 event in 1 patient (bruising, 7%) was judged as severe. No patient discontinued treatment due to injection site reaction or injection site pain.

16 HOW SUPPLIED/STORAGE AND HANDLING

Follistim AQ Cartridge is supplied in a box containing disposable, 29 gauge, ultra-fine, $\frac{1}{2}$ -inch, sterile BD Micro-Fine™ Pen Needles (for use with Follistim Pen available separately) packaged with one disposable 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 international units per 0.210 mL (delivering 150 international units) with orange crimp-caps and 3 BD Micro-Fine Pen Needles
- NDC 0052-0313-01 Follistim AQ Cartridge 350 international units per 0.420 mL (delivering 300 international units) with silver crimp-caps and 5 BD Micro-Fine Pen Needles
- NDC 0052-0316-01 Follistim AQ Cartridge 650 international units per 0.780 mL (delivering 600 international units) with gold crimp-caps and 7 BD Micro-Fine Pen Needles
- NDC 0052-0326-01 Follistim AQ Cartridge 975 international units per 1.170 mL (delivering 900 international units) with blue crimp-caps and 10 BD Micro-Fine Pen Needles

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.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

17.1 Dosing and Use of Follistim AQ Cartridge with Pen

Instruct women and men on the correct usage and dosing of Follistim AQ Cartridge in conjunction with the Follistim Pen. Make sure that individuals who have used other gonadotropin products delivered by a syringe are aware of differences arising from use of the pen. Women and men should read and follow all instructions in the Follistim Pen "Instructions for Use" Manual prior to administration of Follistim AQ Cartridge.

Advise women and men of the number of doses which can be extracted from the full unused Follistim AQ Cartridge that you have prescribed.

17.2 Therapy Duration and Necessary Monitoring in Women and Men Undergoing Treatment

Prior to beginning therapy with Follistim AQ Cartridge, inform women and men about the time commitment and monitoring procedures necessary to undergo treatment [see *Dosage and Administration* (2)].

17.3 Instructions on a Missed Dose

Inform women and men that if they miss or forget to take a dose of Follistim AQ Cartridge, the next dose should not be doubled and they should call the healthcare provider for further dosing instructions.

17.4 Ovarian Hyperstimulation Syndrome

Inform women regarding the risks with use of Follistim AQ Cartridge of Ovarian Hyperstimulation Syndrome. Instruct women to call their healthcare provider immediately if they have pain in the lower abdomen, nausea, vomiting, sudden weight gain, diarrhea, decreased urine output, or trouble breathing. [See *Warnings and Precautions* (5.2).]

17.5 Ovarian Torsion

Inform women regarding the risks of ovarian torsion with use of Follistim AQ Cartridge. Instruct women to call their healthcare provider immediately if they have pain in the lower abdomen. [See *Warnings and Precautions* (5.4).]

17.6 Adverse Events Reported During the Course of Treatment with IVF or ICSI

Inform women that the following have been reported during the course of treatment with IVF or ICSI:

- pulmonary and vascular complications *[See Warnings and Precautions (5.3).]*
- risk of multi-fetal gestation and birth *[See Warnings and Precautions (5.5).]*
- congenital anomalies *[See Warnings and Precautions (5.6).]*
- ectopic pregnancy *[See Warnings and Precautions (5.7).]*
- spontaneous abortion *[See Warnings and Precautions (5.8).]*
- ovarian and other reproductive system neoplasms *[See Warnings and Precautions (5.9).]*

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MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by: Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany

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Revised: 09/2019

uspi-mk8328-SOI-1909r013