HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GONAL-F RFF® safely and effectively. See full prescribing information for GONAL-F RFF® (follitropin alfa for injection) for subcutaneous use
Initial U.S. Approval: 1997

RECENT MAJOR CHANGES

Dosage and Administration	12/20
Contraindications (4)	12/20
Warnings and Precautions	
Hypersensitivity Reactions and Anaphylaxis (5.1)	12/20
Ovarian Hyperstimulation Syndrome (OHSS) (5.2)	12/20
Pulmonary and Vascular Complications (5.3)	12/20
Ovarian Torsion (5.4)	12/20
Abnormal Ovarian Enlargement (5.5)	12/20
Embryofetal Toxicity (5.7)	12/20
Ectopic Pregnancy (5.8)	12/20
Spontaneous Abortion (5.9)	12/20
Ovarian Neoplasms (5.10)	12/20

INDICATIONS AND USAGE

GONAL-F RFF is a gonadotropin indicated for:

- Induction of ovulation and pregnancy in oligo-anovulatory infertile women for whom the cause of infertility is functional and not due to primary ovarian failure. (1.1)
- Development of multiple follicles in ovulatory infertile women as part of Assisted Reproductive Technology (ART) cycles. (1.2)

DOSAGE AND ADMINISTRATION

Induction of Ovulation (2.2)

- Initial starting dose of the first cycle: 75 International Units of GONAL-F RFF per day for 14 days, administered subcutaneously
- Individualize doses after 14 days
- Do not administer doses greater than 300 International Units per day

Development of Multiple Follicles in Assisted Reproductive Technology (ART) (2.3)

- Initial starting dose of the first cycle: 150 International Units per day, administered subcutaneously
- Dosage adjustments after 3 to 5 days and by 75 to 150 International Units at each adjustment
- Do not administer doses greater than 450 International Units per day

DOSAGE FORMS AND STRENGTHS

- For Injection: 82.5 International Units lyophilized powder in a single-dose vial for reconstitution. A 1 mL prefilled syringe of Sterile Water for Injection, USP is included for reconstitution to deliver 75 International Units of follitropin alfa. (3)

CONTRAINDICATIONS

GONAL-F RFF is contraindicated in women who exhibit (4):

- Prior hypersensitivity to recombinant FSH products or one of their excipients
- High levels of FSH indicating primary gonadal failure
- Uncontrolled non-gonadal endocrinopathies
- Sex hormone dependent tumors of the reproductive tract and accessory organs
- Tumors of the pituitary gland or hypothalamus
- Abnormal uterine bleeding of undetermined origin
- Ovarian cyst or enlargement of undetermined origin

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions and Anaphylaxis: If occurs, initiate appropriate therapy, including supportive measures, and discontinue use of GONAL-F RFF (5.1)
- Ovarian Hyperstimulation Syndrome (OHSS): If serious, stop gonadotropins, including hCG, and determine if the woman needs to be hospitalized. Treatment is primarily symptomatic and consists of bed rest, fluid and electrolyte management, and analgesics (5.2)
- Pulmonary and Vascular Complications: In women with recognized risk factors, the benefits of induction of ovulation and ART need to be weighed against the risks. During or after use of GONAL-F RFF, monitor for venous or arterial thromboembolic events (5.3)
- Ovarian Torsion: Early diagnosis and immediate detorsion limit damage to the ovary due to reduced blood supply (5.4)
- Abnormal Ovarian Enlargement: If the ovaries are abnormally enlarged on the last day of GONAL-F RFF therapy, inform women not to administer hCG and to avoid intercourse (5.5)
- Multi-fetal Gestation and Births: The rate of multiple births is dependent on the number of embryos transferred. Advise the woman and her partner of the potential risk of multi-fetal gestation and birth before beginning therapy with GONAL-F RFF (5.6)
- Embryofetal Toxicity: Inform women that the incidence of congenital malformations (birth defects) after some Assisted Reproductive Technology [(ART) specifically in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)] may be slightly higher than after spontaneous conception. There is no evidence that the use of gonadotropins during IVF or ICSI is associated with an increased risk of congenital malformations (5.7)
- Ectopic Pregnancy: Advise women who become pregnant following ART and have: abdominal/pelvic pain (particularly on one side); shoulder, neck or rectal pain; and nausea and vomiting to seek immediate medical attention. Confirm the presence of an intrauterine pregnancy early by β-hCG testing and transvaginal ultrasound (5.8)
- Spontaneous Abortion: The risk of spontaneous abortion (miscarriage) is increased with gonadotropin products, however, causality has not been established (5.9)
- Ovarian Neoplasm: Both benign and malignant ovarian neoplasms are reported in women who have had multiple drug therapy for controlled ovarian stimulation, however, causality has not been established (5.10)

ADVERSE REACTIONS

- The most common adverse reactions (≥2%) in ovulation induction include: headache, abdominal pain, ovarian hyperstimulation, injection site pain, diarrhea, flatulence nausea, ovarian cyst, and injection site inflammation (6.1)
- The most common adverse reactions (≥2%) in development of multiple follicles in ART include: abdominal pain, headache, abdominal enlargement, injection site bruising, nausea, injection site pain, ovarian hyperstimulation, injection site inflammation, injection site reaction, and injection site edema (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact EMD Serono at 1-800-283-8088 ext 5563 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Lactation: Advise not to breastfeed (8.2)

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

Revised: 12/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Gonal-F RFF is indicated for:

1.1 Induction of ovulation and pregnancy in oligo-anovulatory infertile women for whom the cause of infertility is functional and not due to primary ovarian failure.

1.2 Development of multiple follicles in ovulatory infertile women as part of an assisted reproductive technology (ART) cycle.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

Only physicians who are experienced in infertility treatment, should treat women with GONAL-F RFF. GONAL-F RFF is a gonadotropins product capable of causing in women, Ovarian Hyperstimulation Syndrome (OHSS) with or without pulmonary or vascular complications *[see Warnings and Precautions (5.2, 5.3,)]* and multiple births *[see Warnings and Precautions (5.6)]*. Gonadotropin therapy requires the availability of appropriate monitoring facilities *[see Warnings and Precautions (5.11)]*. Use the lowest effective dose of GONAL-F RFF.

Give careful attention to the diagnosis of infertility and the selection of candidates for GONAL-F RFF therapy *[see Dosage and Administration (2.3, 2.4)]*.

2.2 Preparation of GONAL-F RFF and Selection of Injection Site

- Store lyophilized vials refrigerated or at room temperature (2°-25°C/36°-77°F) and protected from light.
- Prior to administration, visually inspect parenteral drug products for particulate matter and discoloration, whenever solution and container permit.
- Following reconstitution of the contents of a single-use vial of GONAL-F RFF into a pre-filled syringe containing 1 mL Sterile Water for Injection, USP, the syringe will deliver 75 International Units of follitropin alfa.
- Dissolve contents of one or more single-use vials of GONAL-F RFF in 1 mL of Sterile Water for Injection, USP (concentration not to exceed 450 International Units/mL).
- An 18-gauge needle is provided for reconstitution. Remove the needle and replace with a 29-gauge needle for injection.
- Discard any unused reconstituted material (Do not store).
- Administer GONAL-F RFF subcutaneously in the abdomen, upper arm, or upper leg as described in Patient Information and Instructions for Use.

2.3 Dosing for Induction of Ovulation

Prior to initiation of treatment with GONAL-F RFF:

- Perform a complete gynecologic and endocrinologic evaluation
- Exclude primary ovarian failure
- Exclude the possibility of pregnancy
- Demonstrate tubal patency
- Evaluate the fertility status of the male partner

The dosing scheme is stepwise and is individualized for each woman *[see Clinical Studies (14.1)]*. Starting doses less than 37.5 International Units have not been studied in clinical trials and are not recommended.

- Administer a starting dose of 75 International Units of GONAL-F RFF subcutaneously daily for 14 days in the first cycle of use.
- In subsequent cycles of treatment, determine the starting dose (and dosage adjustments) of GONAL-F RFF based on the woman's history of the ovarian response to GONAL-F RFF.
- If indicated by the ovarian response after the initial 14 days, make an incremental adjustment in dose, up to 37.5 International Units.
- If indicated by the ovarian response, make additional incremental adjustments in dose, up to 37.5 International Units, every 7 days.
- Continue treatment until follicular growth and/or serum estradiol levels indicate an adequate ovarian response.
- Consider the following when planning the woman's individualized dose:
    - Use the lowest dose of GONAL-F RFF consistent with the expectation of good results.
    - Use appropriate GONAL-F RFF dose adjustment(s) to prevent multiple follicular growth and cycle cancellation.
    - The maximum, individualized, daily dose of GONAL-F RFF is 300 International Units per day.
    - In general, do not exceed 35 days of treatment.
- Discontinue GONAL-F RFF treatment, if the ovaries are abnormally enlarged or abdominal pain occurs.
- When pre-ovulatory conditions are reached, administer human chorionic gonadotropin (hCG) to induce final oocyte maturation and ovulation.
- Encourage the woman and her partner to have intercourse daily, beginning on the day prior to the administration of hCG and until ovulation becomes apparent.
- Withhold hCG in cases where the ovarian monitoring suggests an increased risk of ovarian hyperstimulation syndrome (OHSS) on the last day of GONAL-F RFF therapy (for example estradiol greater than 2,000 pg per mL) *[see Warnings and Precautions (5.2 5.3, 5.5, 5.11)]*.
    - Discourage intercourse when the risk for OHSS is increased [see Warnings and Precautions (5.2, 5.5)].

- Individualize the initial dose administered in subsequent cycles based on the woman's response in the preceding cycle.
- As in the initial cycle, do not administer doses larger than 300 International Units of FSH per day.
- Follow the above recommendations to minimize the chance of development of OHSS.

2.4 Dosing for Multiple Follicle Development as part of an Assisted Reproductive Technology (ART) Cycle

Prior to initiation of treatment with GONAL-F RFF:

- Perform a complete gynecologic and endocrinologic evaluation, and diagnose the cause of infertility
- Exclude the possibility of pregnancy
- Evaluate the fertility status of the male partner

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

- Beginning on cycle day 2 or 3, administer subcutaneously a starting dose of 150 International Units of GONAL-F RFF daily until sufficient follicular development, as determined by ultrasound in combination with measurement of serum estradiol levels, is attained. In most cases, therapy should not exceed 10 days.
  In women under 35 years of age whose endogenous gonadotropin levels are suppressed, initiate GONAL-F RFF administration at a dose of 150 International Units per day.
  In women 35 years of age and older whose endogenous gonadotropin levels are suppressed, initiate GONAL-F RFF administration at a dose of 225 International Units per day.
- Adjust the dose after 5 days based on the woman's ovarian response, as determined by ultrasound evaluation of follicular growth and serum estradiol levels.
- Do not make additional dosage adjustments more frequently than every 3-5 days or by more than 75-150 International Units at each adjustment.
- Continue treatment until adequate follicular development is evident, and then administer hCG to induce final follicular maturation in preparation for oocyte retrieval.
- Withhold hCG administration in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of GONAL-F RFF therapy *[see Warnings and Precautions (5.2, 5.3, 5.5, 5.11)].*
- Do not use doses greater than 450 International Units per day.

2.5 Missed Dose

Do not double the next dose if the woman misses or forgets to take a dose of GONAL-F RFF.

3 DOSAGE FORMS AND STRENGTHS

For injection: 82.5 International Units of follitropin alpha as a lyophilized powder in a single dose vial for reconstitution, including a 1 mL pre-filled syringe of Sterile Water for Injection, USP for reconstitution to deliver 75 International Units of follitropin alfa.

4 CONTRAINDICATIONS

GONAL-F RFF is contraindicated in women who exhibit:

- Prior hypersensitivity to recombinant FSH products or one of their excipients. Reactions have included anaphylaxis *[see Warnings and Precautions (5.1)].*

- High levels of FSH indicating primary gonadal failure
- The presence of uncontrolled non-gonadal endocrinopathies (for example, thyroid, adrenal, or pituitary disorders)
- Sex hormone dependent tumors of the reproductive tract and accessory organs
- Tumors of the pituitary gland or hypothalamus
- Abnormal uterine bleeding of undetermined origin
- Ovarian cyst or enlargement of undetermined origin

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions and Anaphylaxis

In the postmarketing experience, serious systemic hypersensitivity reactions, including anaphylaxis, have been reported with use of GONAL-F® and GONAL-F® RFF. Symptoms have included dyspnea, facial edema, pruritus, and urticaria. If an anaphylactic or other serious allergic reaction occurs, initiate appropriate therapy including supportive measures if cardiovascular instability and/or respiratory compromise occur, and discontinue further use.

5.2 Ovarian Hyperstimulation Syndrome (OHSS)

Ovarian Hyperstimulation Syndrome (OHSS) is a medical event 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 the development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. Abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement *[see Warnings and Precautions (5.5)]*, weight gain, dyspnea, and oliguria have been reported with OHSS. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic reactions *[See Warnings and Precautions (5.3)]*. Transient liver function test abnormalities suggestive of hepatic dysfunction with or without morphologic changes on liver biopsy, have been reported in association with OHSS.

OHSS occurs after gonadotropin 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 Dosage and Administration (2.3, 2.4)]*, withhold hCG. Cases of OHSS are more common, more severe, and more protracted if pregnancy occurs; therefore, assess women for the development of OHSS for at least two weeks after hCG administration.

If serious OHSS occurs, stop gonadotropins, including GONAL-F RFF and hCG, and consider whether the woman needs to be hospitalized. Treatment is primarily symptomatic and overall consists of bed rest, fluid and electrolyte management, and analgesics (if needed). Because the use of diuretics can accentuate the diminished intravascular volume, avoid diuretics except in the late phase of resolution as described below. The management of OHSS is divided into three phases as follows:

- Acute Phase:

Management is directed at preventing hemoconcentration due to loss of intravascular volume to the third space and minimizing the risk of thromboembolic phenomena and kidney damage. Thoroughly assess daily or more often, based on the clinical need, fluid intake and output, weight, hematocrit, serum and urinary electrolytes, urine specific gravity, BUN and creatinine, total proteins with albumin: globulin ratio, coagulation studies, electrocardiogram to monitor for hyperkalemia, and abdominal girth. Treatment, consisting of limited intravenous fluids, electrolytes, human serum albumin, 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.

- Chronic Phase:

  After the acute phase is successfully managed as above, excessive fluid accumulation in the third space should be limited by instituting severe potassium, sodium, and fluid restriction.

- Resolution Phase:

  As third space fluid returns to the intravascular compartment, a fall in hematocrit and increasing urinary output are observed in the absence of any increase in intake. 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.

  Do not remove ascitic, pleural, and pericardial fluid, unless there is the necessity to relieve symptoms such as pulmonary distress or cardiac tamponade.

OHSS increases the risk of injury to the ovary. Avoid pelvic examination or intercourse, as these may cause rupture of an ovarian cyst, which may result in hemoperitoneum.

If bleeding occurs and requires surgical intervention, control the bleeding and retain as much ovarian tissue as possible. A physician experienced in the management of this syndrome, or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

OHSS occurred in 6 of 83 (7.2%) GONAL-F RFF treated women in an induction of ovulation trial; none were classified as severe. In an ART trial, OHSS occurred in 11 of 237 (4.6%) GONAL-F RFF treated women and 1 (0.42%) was classified as severe.

5.3 Pulmonary and Vascular Complications

Serious pulmonary conditions (for example, atelectasis, acute respiratory distress syndrome and exacerbation of asthma) have been reported in women treated with gonadotropins, including GONAL-F RFF. In addition, thromboembolic events both in association with, and separate from OHSS have been reported in women treated with gonadotropins, including GONAL-F RFF. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Women with generally recognized risk factors for thrombosis, such as 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. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb and rarely in myocardial infarctions. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death. In

women with recognized risk factors, the benefits of ovulation induction and Assisted Reproductive Technology (ART) need to be weighed against the risks. It should be noted that pregnancy also carries an increased risk of thrombosis.

5.4 Ovarian Torsion

Ovarian torsion has been reported after treatment with gonadotropins, including

GONAL-F RFF. This may be related to OHSS, pregnancy, previous abdominal surgery, past history of ovarian torsion, previous or current ovarian cyst and polycystic ovaries. Early diagnosis and immediate detorsion limit damage to the ovary due to reduced blood supply.

5.5 Abnormal Ovarian Enlargement

In order to minimize the hazards associated with abnormal ovarian enlargement that may occur with GONAL-F RFF therapy, individualize treatment and use the lowest effective dose *[see Dosage and Administration (2.3, 2.4)]*. Use of ultrasound monitoring of ovarian response and/or measurement of serum estradiol levels is important to minimize the risk of ovarian stimulation *[see Warnings and Precautions (5.12)]*.

If the ovaries are abnormally enlarged on the last day of GONAL-F RFF therapy, do not administer hCG in order to reduce the chance of developing OHSS *[see Warnings and Precautions (5.2)]*. Prohibit intercourse for women with significant ovarian enlargement after ovulation because of the danger of hemoperitoneum resulting from rupture of ovarian cysts *[see Warnings and Precautions (5.2)].*

5.6 Multi-fetal Gestation and Birth

Multi-fetal gestation and births have been reported with all gonadotropin therapy, including therapy with GONAL-F RFF. In a trial of induction of ovulation, 20% of live births were multiple births in women receiving GONAL-F RFF over three treatment cycles.

In an ART trial, 35.1% of live births were multiple births in women receiving GONAL-F RFF. The rate of multiple births is dependent on the number of embryos transferred. Advise the woman and her partner of the potential risk of multi-fetal gestation and birth before beginning therapy with GONAL-F RFF.

5.7 Embryofetal Toxicity

The incidence of congenital malformations (birth defects) after some Assisted Reproductive Technology [(ART) specifically in vitro fertilization (IVF) or intracytoplasmic sperm injection (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, maternal and paternal genetic background, sperm characteristics) and to the higher incidence of multi-fetal gestations after IVF or ICSI. There is no evidence that the use of gonadotropins during IVF or ICSI is associated with an increased risk of congenital malformations.

5.8 Ectopic Pregnancy

Since infertile women undergoing ART often have tubal abnormalities, the incidence of ectopic pregnancy may be increased in women who become pregnant as a result of ART. Advise women who become pregnant following ART and have: abdominal/pelvic pain (particularly on one side); shoulder, neck or rectal pain; and nausea and vomiting to

seek immediate medical attention. Confirm the presence of an intrauterine pregnancy early by β-hCG testing and transvaginal ultrasound.

5.9 Spontaneous Abortion

The risk of spontaneous abortion (miscarriage) is increased with gonadotropin products, including GONAL-F RFF. However, causality has not been established. The increased risk may be a factor of the underlying infertility.

5.10 Ovarian Neoplasms

There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have had multiple drug therapy for controlled ovarian stimulation, however, a causal relationship has not been established.

5.11 Laboratory Tests

In most instances, treatment of women with GONAL-F RFF results only in follicular recruitment and development. In the absence of an endogenous LH surge, hCG is given to trigger ovulation when monitoring of the patient indicates that sufficient follicular development has occurred. This may be estimated by ultrasound alone or in combination with measurement of serum estradiol concentrations. The combination of both ultrasound and serum estradiol measurement are useful for monitoring follicular growth and maturation, timing of the ovulatory trigger, detecting ovarian enlargement and minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation.

The clinical confirmation of ovulation is obtained by direct or indirect indices of progesterone production, as well as sonographic evidence of ovulation.

Direct or indirect indices of progesterone production:

- Urinary or serum luteinizing hormone (LH) rise
- A rise in basal body temperature
- Increase in serum progesterone
- Menstruation following a shift in basal body temperature

Sonographic evidence of ovulation:

- Collapsed follicle
- Fluid in the cul-de-sac
- Features consistent with corpus luteum formation
- Secretory endometrium

6 ADVERSE REACTIONS

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

- Hypersensitivity Reactions and Anaphylaxis *[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)]*
- Abnormal Ovarian Enlargement *[see Warnings and Precautions (5.5)]*
- Multi-fetal Gestation and Birth *[see Warnings and Precautions (5.6)]*
- Embryofetal Toxicity *[see Warnings and Precautions (5.7)]*

- Ectopic Pregnancy *[see Warnings and Precautions (5.8)]*
- Spontaneous Abortion *[see Warnings and Precautions (5.9)]*
- Ovarian Neoplasms *[see Warnings and Precautions (5.10)]*

6.1 Clinical Study Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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.

The safety of GONAL-F RFF was examined in two clinical trials (one Ovulation Induction trial and one ART trial).

Induction of Ovulation
In a multiple cycle (a maximum of three cycles), assessor-blind, multinational, multicenter, active-comparator trial versus a recombinant FSH comparator, a total of 83 oligo-anovulatory infertile women were randomized and underwent induction of ovulation with GONAL-F RFF. Adverse reactions occurring in at least 2.0% of women receiving GONAL-F RFF are listed in Table 1.

Table 1: Common Adverse Reactions Reported at a Frequency of ≥ 2% in an Ovulation Induction Trial

System Organ Class/Adverse Reactions	**GONAL-F RFF [N=83[a] (176 treatment cycles[b])] n[c] (%)**
Central and Peripheral Nervous System	
Headache	22 (26.5%)
Gastrointestinal System	
Abdominal Pain	10 (12.0%)
Nausea	3 (3.6%)
Flatulence	3 (3.6%)
Diarrhea	3 (3.6%)
Reproductive, Female	

Ovarian Hyperstimulation	6 (7.2%)
Ovarian Cyst	3 (3.6%)
Application Site	
Injection Site Pain	4 (4.8%)
Injection Site Inflammation	2 (2.4%)

[a] total number of women treated with GONAL-F RFF
[b] up to 3 treatment cycles per woman
[c] number of women with the adverse reaction

Development of Multiple Follicles as part of an Assisted Reproductive Technology (ART) Cycle
In a single cycle, assessor-blind, multinational, multicenter, active-comparator trial versus a recombinant FSH comparator, a total of 237 normal ovulatory infertile women were randomized and received GONAL-F RFF as part of an ART [in vitro fertilization (IVF) or intracytoplasmic sperm injection cycle (ICSI)] cycle. All women received pituitary down-regulation with gonadotropin releasing hormone (GnRH) agonist before stimulation. Adverse Reactions occurring in at least 2.0% of women are listed in Table 2.

Table 2: Common Adverse Reactions Reported at a Frequency of ≥ 2% in an Assisted Reproductive Technologies Trial

System Organ Class/Adverse Reactions	**GONAL-F RFF (N=237[a]) n[b] (%)**
Gastrointestinal System	
Abdominal Pain	55 (23.2%)
Nausea	19 (8.0%)
Body as a Whole- General	
Abdomen Enlarged	33 (13.9%)
Central and Peripheral Nervous	

System	
Headache	44 (18.6%)
Application Site Disorders	
Injection Site Bruising	23 (9.7%)
Injection Site Pain	13 (5.5%)
Injection Site Inflammation	10 (4.2%)
Injection Site Reaction	10 (4.2%)
Injection Site Edema	6 (2.5%)
Reproductive, Female	
Ovarian Hyperstimulation	11 (4.6%)

[a] total number of women treated with GONAL-F RFF
[b] number of women with the adverse reaction

6.2 Postmarketing Experience

The following adverse reactions have been reported during postapproval use of GONAL-F RFF. 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.

Body as a Whole - General: *Hypersensitivity reactions including anaphylaxis*

Respiratory System: *Asthma exacerbation*

Vascular Disorders: *Thromboembolism*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

GONAL-F RFF is not indicated in pregnant women.

The incidence of congenital malformations after some Assisted Reproductive Technology [(ART), specifically in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)],

may be slightly higher than that after spontaneous conception. This slightly higher incidence is thought to be related to differences in parental characteristics (e.g., maternal age, maternal and paternal genetic background, sperm characteristics) and to a higher incidence of multi-fetal gestations after IVF or ICSI. There is no human data that the use of gonadotropins (including GONAL-F RFF), alone or as part of IVF or ICSI cycles, increases the risk of congenital malformations.

The risk of spontaneous abortion (miscarriage) is increased in women who have used gonadotropins products (including GONAL-F RFF) to achieve pregnancy.

In animal studies, the continuous administration of recombinant human FSH during pregnancy resulted in a decrease in the number of viable fetuses and difficult and prolonged delivery. No teratogenic effect has been observed.

In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Data on a limited number of GONAL-F RFF- or GONAL-F-exposed pregnancies indicate no adverse reactions of gonadotropins on pregnancy, embryonal or fetal development, parturition or postnatal development following controlled ovarian stimulation.

Animal Data

Embryofetal development studies with recombinant human FSH in rats, where dosing occurred during organogenesis, showed a dose dependent increase in difficult and prolonged parturition in dams, and dose dependent increases in resorptions, pre- and post-implantation losses, and stillborn pups at doses representing 5 and 41 times the lowest clinical dose of 75 International Units based on body surface area. Pre-/post-natal development studies with recombinant human FSH in rats, where dosing occurred from mid-gestation through lactation, showed difficult and prolonged parturition in all dams dosed at 41 times the lowest clinical dose of 75 International Units based on body surface area, along with maternal death and stillborn pups associated with the difficult and prolonged parturition. This toxicity was not observed in dams and offspring dosed at a level 5 times the lowest clinical dose of 75 International Units based on body surface area.

8.2 Lactation

There are no data on the presence of GONAL-F RFF in human milk, the effects on the breastfed infant, or the effects on milk production. Because the secretion of prolactin during lactation can result in inadequate response to ovarian stimulation, advise women not to breast feed during treatment with GONAL F RFF.

8.3 Females and Males of Reproductive Potential

Because GONAL-F RFF is not indicated in pregnant women, verify a negative pregnancy test before administering GONAL-F RFF to a woman *[see Dosage and Administration (2.3, 2.4)].*

8.4 Pediatric use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Safety and effectiveness of GONAL-F RFF in postmenopausal women have not been established and it is not indicated in this population.

10 OVERDOSAGE

Ovarian hyperstimulation syndrome (OHHS) and multiple gestations have been observed with GONAL-F RFF overdosage *[see Warnings and Precautions (5.2,5.6)]*.

11 DESCRIPTION

GONAL-F RFF (follitropin alpha for injection) is a gonadotropin [human follicle stimulating hormone (FSH)], a glycoprotein hormone manufactured by recombinant DNA technology. The active drug substance, follitropin alfa, has a dimeric structure consisting of two non-covalently linked, non-identical glycoproteins designated as the α- and β-subunits. The α- and β-subunits have 92 and 111 amino acids, respectively, and their primary and tertiary structure are indistinguishable from those of human follicle stimulating hormone.

Recombinant human FSH production occurs in genetically modified Chinese Hamster Ovary (CHO) cells cultured in bioreactors. Purification by immunochromatography using an antibody specifically binding FSH results in a highly purified preparation with a consistent FSH isoform profile, and a high specific activity. The protein content is assessed by size exclusion high pressure liquid chromatography. The biological activity of follitropin alfa is determined by measuring the increase in ovary weight in female rats. The *in vivo* biological activity of follitropin alfa has been calibrated against the first International Standard for recombinant human follicle stimulating hormone established in 1995 by the Expert Committee on Biological Standards of the World Health Organization. GONAL-F RFF contains no luteinizing hormone (LH) activity. Based on available data derived from physico-chemical tests and bioassays, follitropin alfa and follitropin beta, another recombinant follicle stimulating hormone product, are indistinguishable.

GONAL-F RFF is a sterile, lyophilized powder intended for subcutaneous injection after reconstitution.

Each GONAL-F RFF single-dose vial is filled with 82 International Units (6 μg) follitropin alfa to deliver 75 International Units (5.5 mcg) and contains 30 mg sucrose, 1.11 mg dibasic sodium phosphate dihydrate, 0.45 mg monobasic sodium phosphate monohydrate, 0.1 mg methionine, and 0.05 mg polysorbate 20. Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment. Vials are reconstituted with Sterile Water for Injection, USP.

Under current storage conditions, GONAL-F RFF may contain up to 10% of oxidized follitropin alfa.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of action

GONAL-F RFF stimulates ovarian follicular growth in women who do not have primary ovarian failure. In order to bring about final maturation of the follicle and ovulation in the absence of an endogenous LH surge, human chorionic gonadotropin (hCG) must be given, following the administration of GONAL-F RFF, when monitoring of the patient indicates that sufficient follicular development is achieved.

12.2 Pharmacodynamics

The pharmacodynamics of GONAL-F RFF have not been fully characterized.
There is inter-woman variability in response to follitropin alfa administration.

12.3 Pharmacokinetics

The pharmacokinetics of GONAL-F RFF have not been fully characterized. Follitropin alfa mean (%CV) AUC_{last} is 884 International Units hr/L (20%) and C_{max} is 9.83 International Units/L (23%) following a single subcutaneous dose of 300 International Units of GONAL-F RFF to 21 pre-menopausal healthy female volunteers who had previously received a GnRH agonist for pituitary down-regulation.

Absorption
The mean (%CV) time to C_{max} is 15.5 hrs (43%).

Elimination
The mean (%CV) elimination half-life of follitropin alfa is 53 hrs (52%) and is dependent on the absorption rate.

Drug Interaction Studies
No studies evaluating the drug interaction potential of follitropin alfa have been conducted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of GONAL-F RFF. However, follitropin alfa showed no mutagenic activity in a series of tests performed to evaluate its potential genetic toxicity including, bacterial and mammalian cell mutation tests, a chromosomal aberration test and a micronucleus test.

Impaired fertility has been reported in rats, exposed to pharmacological doses of follitropin alfa (greater than or equal to 40 International Units per kg per day, greater than or equal to 5 times the lowest clinical dose of 75 International Units) for extended periods, through reduced fecundity.

14 CLINICAL STUDIES

14.1 Induction of Ovulation (OI):

Induction of Ovulation was evaluated in a randomized, assessor-blind, multinational, multicenter, active-controlled trial in oligo-anovulatory infertile women. Women were randomized to either GONAL-F RFF (n=83), administered subcutaneously, or a comparator recombinant human FSH product. The use of insulin-sensitizing agents was allowed during the trial. The trial was designed to evaluate and compare mean ovulation rates in the first cycle of treatment. Results for GONAL-F RFF are presented in Table 3. Also presented in this table are secondary outcome results from cycle 1 through 3. The trial was not powered to demonstrate differences in any of the secondary outcomes.

Table 3: Cumulative Ovulation and Clinical Pregnancy Rates in Induction of Ovulation

Cycle	GONAL-F RFF (n=83)	
	Cumulative[a] Percent Ovulation	Cumulative[a] Clinical Pregnancy[d] Rate
Cycle 1	72%[b]	28%[c]
Cycle 2	89%[c]	41%[c]
Cycle 3	92%[c]	45%[c]

[a]Cumulative rates were determined per woman over cycles 1, 2, and 3.
[b]Non-inferior to comparator recombinant human FSH based on a two-sided 95% confidence interval, intent-to-treat analysis.
[c]Secondary efficacy outcomes. The trial was not powered to demonstrate differences in these outcomes.
[d]Clinical pregnancy was defined as a pregnancy for which a fetal sac (with or without heart activity) was visualized by ultrasound on day 34-36 after hCG administration.

14.2. Development of Multiple Follicles as part of an Assisted Reproductive Technology (ART) Cycle:

The efficacy of GONAL-F RFF was evaluated in a randomized, assessor-blind, multinational, multicenter active-controlled trial in ovulatory, infertile women treated for one cycle with controlled ovarian stimulation as part of an ART [in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI)] cycle. Women were randomized to either GONAL-F RFF (n=237), administered subcutaneously, or a comparator recombinant human FSH product. Randomization was stratified by insemination technique (IVF versus ICSI). All women received a GnRH agonist for pituitary down-regulation before receiving stimulation with recombinant FSH. The primary endpoint was the mean number of fertilized oocytes the day after insemination. The initial doses of GONAL-F RFF were 150 International Units per day for women less than 35 years of age and 225 International Units per day for women 35 years of age and older. The maximal dose given for both age groups was 450 International Units per day. Treatment outcomes for GONAL-F RFF are summarized in Table 4.

Table 4: Treatment Outcomes in ART

Trial Outcome	value (n)
Mean number of 2PN oocytes per woman [a]	6.3 (237)

Mean number of 2PN oocytes per woman receiving IVF [b]	6.1 (88)
Mean number of 2PN oocytes per woman receiving ICSI[b]	6.5 (132)
Clinical pregnancy[c] rate per attempt[d]	33.5% (218)
Clinical pregnancy[c] rate per embryo transfer [d]	35.8% (204)
Mean treatment duration in days (range) [d]	9.7 [3-21] (230)

[a] Non-inferior to comparator recombinant human FSH based on a two-sided 95% confidence interval, intent-to-treat analysis.
[b] Subgroup analyses. The trial was not powered to demonstrate differences in subgroups.
[c] A clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heart activity) was visualized by ultrasound on day 35-42 after hCG administration.
[d] Secondary efficacy outcomes. The trial was not powered to demonstrate differences in these outcomes.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 HOW SUPPLIED

GONAL-F RFF (follitropin alfa for injection) is supplied in a sterile, lyophilized white powder in single-dose vials containing 82 International Units with diluent (Sterile Water for Injection, USP) in a pre-filled syringe. Following reconstitution with the diluent as described, upon administration each vial will deliver a dose of 75 International Units.

The following package combinations are available:
1 vial GONAL-F RFF 75 International Units and 1 pre-filled syringe Sterile Water for Injection, USP, 1 mL, 1 reconstitution needle (18 gauge), 1 administration needle (29 gauge), NDC 44087-9005-1

10 vials GONAL-F RFF 75 International Units and 10 pre-filled syringes Sterile Water for Injection, USP, 1 mL, 10 reconstitution needles (18 gauge), 10 administration needles (29 gauge), NDC 44087-9005-6

16.2 STORAGE AND HANDLING

Lyophilized vials may be stored refrigerated or at room temperature (2°-25°C/36°-77°F). Protect from light. Use immediately after reconstitution *[see Dosage and Administration (2.2)]*.

Sterile Water for Injection, USP is provided in a pre-filled syringe. Separate needles are provided for reconstitution (18 G) and administration (29 G).

Note: No antimicrobial or other substance has been added to the Sterile Water for Injection for the single-dose vials. Sterile Water for Injection is not suitable for intravascular injection without its first having been made approximately isotonic by the addition of a suitable solute.

17 PATIENT COUNSELING INFORMATION

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

Hypersensitivity Reactions and Anaphylaxis

Advise women to discontinue Gonal-F RFF and seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur *[see Warnings and Precautions (5.1)].*

Ovarian Hyperstimulation Syndrome

Inform women regarding the risks of OHSS *[see Warnings and Precautions (5.2)]* and OHSS-associated conditions including pulmonary and vascular complications *[see Warnings and Precautions (5.3)],* and ovarian torsion *[see Warnings and Precautions (5.4)]* with the use of GONAL-F RFF. Advise women to seek medical attention if any of these conditions occur.

Abnormal Ovarian Enlargement

Inform women regarding the hazards associated with abnormal ovarian enlargement that may occur with GONAL-F RFF therapy. If the ovaries are abnormally enlarged on the last day of GONAL-F RFF therapy, inform women not to administer hCG and to avoid intercourse *[see Warnings and Precautions (5.5)]*.

Multi-fetal Gestation and Birth

Advise the woman and her partner of the potential risk of multi-fetal gestation and birth before beginning therapy with GONAL-F RFF *[see Warnings and Precautions (5.6)]*.

Embryofetal Toxicity

Inform women that the incidence of congenital malformations (birth defects) after some Assisted Reproductive Technology [(ART) specifically in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)] may be slightly higher than after spontaneous conception *[see Warnings and Precautions (5.7)]*.

Ectopic Pregnancy

Inform women undergoing ART that the incidence of ectopic pregnancy may be increased with these procedures, particularly for women with tubal abnormalities. Advise women who become pregnant and have: abdominal/pelvic pain (particularly on one side); shoulder, neck or rectal pain; and nausea and vomiting to seek immediate medical attention *[see Warnings and Precautions (5.8)]*.

Spontaneous Abortion

Inform women that the risk of spontaneous abortion (miscarriage) is increased with gonadotropin products (including GONAL-F RFF). However, causality has not been established. The increased risk may be a factor of the underlying infertility *[see Warnings and Precautions (5.9)]*.

Lactation

Advise women not to breastfeed because the secretion of prolactin during lactation can result in inadequate response to ovarian stimulation with Gonal-F RFF [see Use in Specific Populations (8.2)].

Dosing and Use of GONAL-F RFF single-use vials
Instruct women on the correct usage and dosing of GONAL-F RFF *[see Dosage and Administration (2.3, 2.4)]*. Instruct women to reconstitute one or more vials of GONAL-F RFF using 1 mL sterile diluent and the 18G 1-1/2" pink mixing needle provided. Instruct women to safely remove mixing needle and replace with 29G ½" needle for injection. Caution women not to change the dosage or the schedule of administration unless she is told to do so by her healthcare provider.

Duration and Necessary Monitoring in Women Undergoing Therapy with GONAL-F RFF
Prior to beginning therapy with GONAL-F RFF, inform women about the time commitment and monitoring procedures necessary for treatment *[see Dosage and Administration (2.3, 2.4) and Warnings and Precautions (5.11)].*

Instructions Regarding a Missed Dose
Inform the woman that if she misses or forgets to take a dose of GONAL-F RFF, she should not double the next dose and should call her healthcare provider for further dosing instructions *[see Dosage and Administration (2.5)].*

Manufactured for:
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