HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use Gonal-f® RFF Redi-ject® safely and effectively. See full prescribing information for Gonal-f® RFF Redi-ject®

Gonal-f® RFF Redi-ject® (follitropin alfa) injection for subcutaneous use

Initial U.S. Approval: 1997

INDICATIONS AND USAGE

Gonal-f® RFF Redi-ject® is a prefilled gonadotropin-containing auto-injection device indicated for:

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

DOSAGE AND ADMINISTRATION

Ovulation Induction (2.2)

- Initial starting dose of the first cycle - 75 International Units of Gonal-f® RFF Redi-ject® per day for 14 days, administered subcutaneously
- Individualization doses after 14 days
- Doses larger than 300 International Units of FSH per day are not recommended

Assisted Reproductive Technology (2.3)

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

DOSAGE FORMS AND STRENGTHS

- Injection: Gonal-f® RFF Redi-ject® 300 International Units per 0.5 mL in prefilled, single-patient-use pen (3)
- Injection: Gonal-f® RFF Redi-ject® 450 International Units per 0.75 mL in prefilled, single-patient-use pen (3)
- Injection: Gonal-f® RFF Redi-ject® 900 International Units per 1.5 mL in prefilled single-patient-use pen (3)

CONTRAINDICATIONS

Gonal-f® RFF Redi-ject® is contraindicated in women who exhibit (4):

- Hypersensitivity to recombinant FSH preparations 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 organ.
- Tumors of pituitary gland or hypothalamus
- Abnormal uterine bleeding of undetermined origin
- Ovarian cyst or enlargement of undetermined origin, not due to polycystic ovary syndrome

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions and Anaphylaxis (5.1)
- Abnormal Ovarian Enlargement (5.2)
- Ovarian Hyperstimulation Syndrome (5.3)
- Pulmonary and Vascular Complications (5.4)
- Ovarian Torsion (5.5)
- Multi-fetal Gestation and Births (5.6)
- Congenital Malformation (5.7)
- Ectopic Pregnancy (5.8)
- Spontaneous Abortion (5.9)
- Ovarian Neoplasms (5.10)

ADVERSE REACTIONS

- The most common adverse reactions (≥5%) in ovulation induction include: headache, abdominal pain, ovarian hyperstimulation (6.1)
- The most common adverse reactions (≥5%) in ART include: abdominal pain, nausea, abdominal enlargement, headache, injection site bruising (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

- Do not use Gonal-f® RFF Redi-ject® in pregnant women (4, 8.1),
- Nursing Mothers: It is not known whether this drug is excreted in human milk. (8.3)
- Pediatric Use: Safety and efficacy not established. (8.4)
- Renal and Hepatic Insufficiency: Safety, efficacy, and pharmacokinetics of Gonal-f® RFF Redi-ject® in women with renal or hepatic insufficiency have not been established. (8.6)

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

Revised: 5/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Induction of Ovulation and Pregnancy in Oligo-Anovulatory Women in whom the Cause of Infertility is Functional and Not Due to Primary Ovarian Failure.

Prior to initiation of treatment with Gonal-f® RFF Redi-ject®:

- 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

1.2 Development of Multiple Follicles in Ovulatory Women as Part of an Assisted Reproductive Technology (ART) Cycle.

Prior to initiation of treatment with Gonal-f® RFF Redi-ject®:

- 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

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.
- Gonal-f® RFF Redi-ject® is a pre-filled disposable auto-injection device intended for multiple dose use.
- Gonal-f® RFF Redi-ject® can be set in 12.5 International Units increments.
- Administer Gonal-f® RFF Redi-ject® subcutaneously in the abdomen as described in Instructions for Use
- Do not attempt to mix any other medications inside of the device with Gonal-f® RFF Redi-ject®.
- Instruct women to remove the Gonal-f® RFF Redi-ject® from the refrigerator at least 30 minutes prior to use in order to allow Gonal-f® RFF Redi-ject® to warm to room temperature and avoid the discomfort of a cold injection.

2.2 Recommended Dosing for Ovulation Induction

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.

- A starting daily dose of 75 International Units of Gonal-f® RFF Redi-ject® is administered subcutaneously daily for 14 days in the first cycle of use.

  In subsequent cycles of treatment, the starting dose (and dosage adjustments) of Gonal-f® RFF Redi-ject® should be determined based on the history of the ovarian response to Gonal-f® RFF Redi-ject®.

- The following should be considered when planning the woman's individualized dose:
  - Appropriate Gonal-f® RFF Redi-ject® dose adjustment(s) should be used to prevent multiple follicular growth and cycle cancellation.
  - The maximum, individualized, daily dose of Gonal-f® RFF Redi-ject® is 300 International Units per day.
  - In general, do not exceed 35 days of treatment.
- 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 adjustments in dose, up to 37.5 International Units, every 7 days.
- Treatment should continue until follicular growth and/or serum estradiol levels indicate an adequate ovarian response.
- When pre-ovulatory conditions are reached, administer human chorionic gonadotropin (hCG) to induce final oocyte maturation and ovulation.

  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 Redi-ject® therapy *[see Warnings and Precautions (5.2, 5.3, 5.11)]*.
- 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.

  Discourage intercourse when the risk for OHSS is increased *[see Warnings and Precautions (5.2, 5.3)]*.

2.3 Recommended Dosing for Assisted Reproductive Technology

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

- Beginning on cycle day 2 or 3, a starting dose of 150 International Units of Gonal-f® RFF Redi-ject® is administered subcutaneously 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 Redi-ject® 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 Redi-ject® 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.

The administration of hCG should be withheld in cases where the ovarian monitoring suggests an increased risk of OHSS on the last day of Gonal-f® RFF Redi-ject® therapy *[see Warnings and Precautions (5.2, 5.3, 5.11)].*

- Doses greater than 450 International Units per day are not recommended.

3 DOSAGE FORMS AND STRENGTHS

Gonal-f® RFF Redi-ject is a clear and colorless to slightly yellow solution available as:

- Injection: Gonal-f® RFF Redi-ject® 300 International Units per 0.5 mL in prefilled, single-patient-use pen
- Injection: Gonal-f® RFF Redi-ject® 450 International Units per 0.75 mL in prefilled, single-patient-use pen
- Injection: Gonal-f® RFF Redi-ject® 900 International Units per 1.5 mL in prefilled, single-patient-use pen

4 CONTRAINDICATIONS

Gonal-f® RFF Redi-ject® is contraindicated in women who exhibit:

- Prior hypersensitivity to recombinant FSH 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)]*
- Sex hormone dependent tumors of the reproductive tract and accessory organs
- Tumors of pituitary gland or hypothalamus
- Abnormal uterine bleeding of undetermined origin
- Ovarian cyst or enlargement of undetermined origin, not due to polycystic ovary syndrome

5 WARNINGS AND PRECAUTIONS

Gonal-f® RFF Redi-ject® should only be used by physicians who are experienced in infertility treatment. Gonal-f® RFF Redi-ject® contains a gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications *[see Warnings and Precautions (5.2, 5.3, 5.4, 5.5)]* and multiple births *[see Warnings and Precautions (5.6)]*. Gonadotropin therapy requires the availability of appropriate monitoring facilities *[see Warnings and Precautions (5.11)]*. The lowest effective dose should be used.

Careful attention should be given to the diagnosis of infertility and the selection of candidates for Gonal-f® RFF Redi-ject® therapy *[see Indications and Usage (1.1, 1.2) and Dosage and Administration (2.2, 2.3)].*

5.1 Hypersensitivity Reactions and Anaphylaxis

Serious systemic hypersensitivity reactions, including anaphylaxis, have been reported in the postmarketing experience with Gonal-f® and Gonal-f® RFF. Symptoms have included dyspnea, facial edema, pruritis, 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 Abnormal Ovarian Enlargement

In order to minimize the hazards associated with abnormal ovarian enlargement that may occur with Gonal-f® RFF Redi-ject® therapy, treatment should be individualized and the lowest effective dose should be used *[see Dosage and Administration (2.2, 2.3)].* 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 (5.11)]*.

If the ovaries are abnormally enlarged on the last day of Gonal-f® RFF Redi-ject® therapy, hCG should not be administered in order to reduce the chance of developing Ovarian Hyperstimulation Syndrome (OHSS) *[see Warnings and Precautions (5.3)]*. Intercourse should be prohibited in women with significant ovarian enlargement after ovulation because of the danger of hemoperitoneum resulting from rupture of ovarian cysts *[see Warnings and Precautions (5.3)]*.

5.3 Ovarian Hyperstimulation Syndrome (OHSS)

OHSS is a medical entity distinct from uncomplicated ovarian enlargement and may progress rapidly to become a serious medical event. OHSS is characterized by a dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of 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, 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 (5.4)]*. 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 Warnings and Precautions (5.2)]*, the hCG must be withheld. Cases of OHSS are more common, more severe, and more protracted if pregnancy occurs; therefore, women should be assessed for the development of OHSS for at least two weeks after hCG administration.

If serious OHSS occurs, gonadotropins, including hCG, should be stopped and consideration should be given as to whether the woman needs to be hospitalized. Treatment is primarily symptomatic and overall should consist of bed rest, fluid and electrolyte management, and analgesics (if needed). Because the use of diuretics can accentuate the diminished intravascular volume, diuretics should be avoided except in the late phase of resolution as described below. The management of OHSS may be divided into three phases as follows:

- *Acute Phase*:
  Management should be directed at preventing hemoconcentration due to loss of intravascular volume to the third space and minimizing the risk of thromboembolic phenomena and kidney damage. 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 should be thoroughly assessed daily or more often based on the clinical need. 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.

Ascitic, pleural, and pericardial fluid should not be removed unless there is the necessity to relieve symptoms such as pulmonary distress or cardiac tamponade.

OHSS increases the risk of injury to the ovary. Pelvic examination or intercourse may cause rupture of an ovarian cyst, which may result in hemoperitoneum, and should therefore be avoided.

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

During clinical trials with Gonal-f® RFF, OHSS occurred in 7.2% of 83 women and 4.6% of 237 women treated with Gonal-f® RFF for ovulation induction and during Assisted Reproductive Technology, respectively.

5.4 Pulmonary and Vascular Complications

Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome and exacerbation of asthma) have been reported in women treated with gonadotropins. 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 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 infarctions. In rare cases, pulmonary complications and/or thromboembolic reactions have resulted in death. In women with recognized risk factors, the benefits of ovulation induction and assisted reproductive technology need to be weighed against the risks. It should be noted that pregnancy also carries an increased risk of thrombosis.

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

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.

During clinical trials with Gonal-f® RFF, multiple births occurred in 20% of live births in women receiving therapy for ovulation induction and 35.1 % of live births in women undergoing ART.

The woman and her partner should be advised of the potential risk of multi-fetal gestation and birth before beginning therapy with Gonal-f® RFF Redi-ject®.

5.7 Congenital Malformations
The incidence of congenital malformations after some 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 are no indications 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. Early confirmation of intrauterine pregnancy should be determined by β-hCG testing and transvaginal ultrasound.

5.9 Spontaneous Abortion
The risk of spontaneous abortion (miscarriage) is increased with gonadotropin products. 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 Redi-ject® will result only in follicular growth and maturation. In the absence of an endogenous LH surge, hCG is given when monitoring of the woman indicates that sufficient follicular development has occurred. This may be estimated by ultrasound alone or in combination with measurement of serum estradiol levels. 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 OHSS 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)]*
- Abnormal Ovarian Enlargement *[see Warnings and Precautions (5.2)]*
- Ovarian Hyperstimulation Syndrome *[see Warnings and Precautions (5.3)]*
- Atelectasis, acute respiratory distress syndrome and exacerbation of asthma *[see Warnings and Precautions (5.4)]*
- Thromboembolic events *[see Warnings and Precautions (5.4)]*
- Ovarian Torsion *[see Warnings and Precautions (5.5)]*
- Multi-fetal Gestation and Birth *[see Warnings and Precautions (5.6)]*
- Congenital Malformations *[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 studies (one ovulation induction study and one ART study).

Ovulation Induction

In a multiple cycle (3), assessor-blind, multinational, multicenter, active comparator study vs. a recombinant FSH comparator, a total of 83 oligo-anovulatory infertile women were randomized and underwent ovulation induction 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 Study

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%)
Neoplasm	
Ovarian Cyst	3 (3.6%)
Reproductive, Female	
Ovarian Hyperstimulation	6 (7.2%)
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

Assisted Reproductive Technology
In a single cycle, assessor-blind, multinational, multicenter, active comparator study vs. 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 Study

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%)

Application 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 postmarketing use of Gonal-f® RFF. Because these reactions were reported voluntarily from a population of uncertain size, the frequency or a causal relationship to Gonal-f® RFF cannot be reliably determined.

Body as a Whole - General: hypersensitivity reactions including anaphylactoid reactions *[see Warnings and Precautions (5.1)]*

Respiratory System: asthma

Vascular disorders: thromboembolism *[see Warnings and Precautions (5.4)]*

7 DRUG INTERACTIONS

No drug-drug interaction studies have been performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Gonal-f® RFF Redi-ject® is not indicated in pregnant women.

The incidence of congenital malformations after some Assisted Reproductive Technology (ART), procedures, 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 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 Redi-ject®), 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 Redi-ject®) 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 after spontaneous clinically recognized pregnancies, is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

Data on a limited number of 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 IU 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 IU 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 IU 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 Redi-ject®.

8.3 Females and Males of Reproductive Potential

Since Gonal-f® RFF Redi-ject® is not indicated in pregnant women, verify a negative pregnancy test before administering Gonal-f® RFF Redi-ject® to a woman *[see Dosage and Administration (2.2, 2.3)]*.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.6 Renal and Hepatic Insufficiency

Safety, efficacy, and pharmacokinetics of Gonal-f® RFF Redi-ject® in women with renal or hepatic insufficiency have not been established.

10 OVERDOSAGE

Aside from possible OHSS *[see Warnings and Precautions (5.3)]* and multiple gestations *[see Warnings and Precautions (5.6)],* there is no additional information on the consequences of acute overdosage with Gonal-f® RFF Redi-ject®.

11 DESCRIPTION

Follitropin alfa, a gonadotropin [human follicle stimulating hormone (hFSH)], is a glycoprotein hormone produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line. It has a dimeric structure consisting of two glycoprotein subunits (alpha and beta). The alpha and beta subunits have 92 and 111 amino acids, respectively, and their primary and tertiary structures are indistinguishable from those of human follicle stimulating hormone. The molecular weight is approximately 31 kDa (14 kDa for alpha subunit and 17 kDa for beta subunit).

Gonal-f® RFF Redi-ject® (follitropin alfa) injection is a sterile, clear and colorless to slightly yellow solution in disposable, prefilled single-patient-use pen intended for the subcutaneous use.

Each Gonal-f® RFF Redi-ject® pen delivers 300 International Units (22 mcg) follitropin alfa in 0.5 mL and the inactive ingredients: dibasic sodium phosphate (0.44 mg), m-cresol (1.5 mg), methionine (0.05 mg), monobasic sodium phosphate (0.196 mg), poloxamer (0.05 mg), sucrose (30 mg) and Water for Injection USP. Phosphoric acid and/or sodium hydroxide may be used to adjust the pH to 7.

Each Gonal-f® RFF Redi-ject® pen delivers 450 International Units (33 mcg) follitropin alfa in 0.75 mL and the inactive ingredients: dibasic sodium phosphate (0.66 mg), m-cresol (2.25 mg), methionine (0.075 mg), monobasic sodium phosphate (0.293 mg), poloxamer (0.075 mg), sucrose (45 mg) and Water for Injection USP. Phosphoric acid and/or sodium hydroxide may be used to adjust the pH to 7.

Each Gonal-f® RFF Redi-ject® pen delivers 900 International Units (66 mcg) follitropin alfa in 1.5 mL and the inactive ingredients: dibasic sodium phosphate (1.33 mg), m-cresol (4.5 mg), methionine (0.15 mg), monobasic sodium phosphate (0.587 mg), poloxamer (0.15 mg), sucrose (90 mg) and Water for Injection USP. Phosphoric acid and/or sodium hydroxide may be used to adjust the pH to 7.

Under current storage conditions, Gonal-f® RFF Redi-ject® may contain up to 10% of oxidized follitropin alfa.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Follicle stimulating hormone (FSH), the active component in Gonal-f® RFF Redi-ject®, is required for normal follicular growth, follicular maturation, and gonadal steroid production. 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.

Gonal-f® RFF Redi-ject® 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 Gonal-f® RFF Redi-ject® when monitoring of the woman indicates that appropriate follicular development parameters have been achieved. There is inter-woman variability in response to FSH administration.

12.3 Pharmacokinetics

Single-dose pharmacokinetics of follitropin alfa were determined following subcutaneous administration of 300 International Units of Gonal-f® RFF Redi-ject® to 21 pre-menopausal healthy female volunteers who were pituitary down-regulated with a GnRH agonist.

The descriptive statistics for the pharmacokinetic parameters are presented in Table 3.

Table 3: Pharmacokinetic parameters of FSH following administration of Gonal-f® RFF Redi-ject® (300 International Units subcutaneously in a single dose)

Parameter	Healthy Volunteers (N=21)	
	Mean	**% CV**
AUC_{last} (IU hr/L)	884	20%
C_{max} (IU/L)	9.83	23%
t_{max} (hr)	15.5	43%
$t_{1/2}$ (hr)	53	52%

Abbreviations are: C_{max}: peak concentration (above baseline)
t_{max}: time of C_{max}
$t_{1/2}$: elimination half life

Absorption

The absorption rate of Gonal-f® RFF Redi-ject® following subcutaneous administration is slower than the elimination rate. Hence, the pharmacokinetics of Gonal-f® RFF Redi-ject® are absorption rate-limited.

Distribution

Human tissue or organ distribution of FSH has not been determined for Gonal-f® RFF Redi-ject®.

Metabolism/Excretion

FSH metabolism and excretion following administration of Gonal-f® RFF Redi-ject® have not been studied in humans.

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 Redi-ject®. 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

The safety and efficacy of Gonal-f® RFF were examined in two clinical studies (one ovulation induction study and one ART study).

14.1 Ovulation Induction (OI)

Ovulation induction was evaluated in a randomized, assessor-blind, multinational, multicenter, active-controlled, study in oligo-anovulatory infertile women. Women were randomized to either Gonal-f® RFF (n=83), administered subcutaneously, or a comparator recombinant human FSH. The use of insulin-sensitizing agents was allowed during the study. The study was designed to evaluate and compare mean ovulation rates in the first cycle of treatment. Results for Gonal-f® RFF are presented in Table 4. Also presented in this table are secondary outcome results from cycle 1 through cycle 3. The study was not powered to demonstrate differences in any of the secondary outcomes.

Table 4: Cumulative Ovulation and Clinical Pregnancy Rates in Ovulation Induction

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 study 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 Assisted Reproductive Technology (ART)

The efficacy of Gonal-f® RFF was evaluated in a randomized, assessor-blind, multinational, multicenter, active controlled study in healthy normal 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. Randomization was stratified by insemination technique, (IVF vs. ICSI). All women received pituitary down-regulation with a GnRH agonist before stimulation with recombinant FSH. Efficacy was assessed using 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 maximum dose given for both age groups was 450 International Units per day. Treatment outcomes for Gonal-f® RFF are summarized in Table 5.

Table 5: Treatment Outcomes in ART

Study Outcome	value (n)
Mean number of 2PN oocytes per woman	6.3 (237)[a]
Mean number of 2PN oocytes per subject receiving IVF	6.1 (88)[b]
Mean number of 2PN oocytes per subject receiving ICSI	6.5 (132)[b]

Clinical pregnancy[c] rate per attempt	33.5% (218)[d]
Clinical pregnancy[c] rate per embryo transfer	35.8% (204)[d]
Mean treatment duration in days (range)	9.7 [3-21] (230)[d]

[a] Non-inferior to comparator recombinant human FSH based on a two-sided 95% confidence interval, intent-to-treat analysis.
[b] Subgroup analyses. The study 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 study was not powered to demonstrate differences in these outcomes.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Gonal-f® RFF Redi-ject® (follitropin alfa) injection is a disposable, prefilled single-patient-use pen containing a clear and colorless to slightly yellow solution. Each Redi-ject® is supplied in a carton containing 29G x 1/2 inch disposable needles to be used for administration.

The following package presentations are available:

NDC 44087-1115-1 - One Gonal-f® RFF Redi-ject® delivers 300 International Units per 0.5 mL and 5 single-use disposable 29G x ½" needles

NDC 44087-1116-1 - One Gonal-f® RFF Redi-ject® delivers 450 International Units per 0.75 mL and 7 single-use disposable 29G x ½" needles

NDC 44087-1117-1 - One Gonal-f® RFF Redi-ject® delivers 900 International Units per 1.5 mL and 14 single-use disposable 29G x ½" needles

16.2 Storage and Handling

Pharmacy Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) until dispensed.

Patient Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) until the expiration date, or store at room temperature at 20° to 25°C (68°F to 77°F) for up to three months or until the expiration date, whichever occurs first. Store pen in the original carton to protect from light. After the first injection, store refrigerated at 2°C to 8°C (36°F to 46°F) or at room temperature at 20°C to 25°C (68°F to 77°F) for up to 28 days. Keep the cap on the pen to protect from light. Do not freeze. Discard unused material after 28 days.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use)

17.1 Dosing and Use of Gonal-f® RFF Redi-ject®

Instruct women on the correct usage and dosing of Gonal-f® RFF Redi-ject® *[see Dosage and Administration (2.2, 2.3)]*. Instruct women to view the dose display in bright light and to adjust the position of the Gonal-f® RFF Redi-ject® to minimize dose window glare. Caution women not to change the dosage or the schedule of administration unless she is told to do so by her healthcare provider. Instruct women to remove the Gonal-f® RFF Redi-ject® from the refrigerator at least 30 minutes prior to use in order to allow Gonal-f® RFF Redi-ject® to warm to room temperature and avoid the discomfort of a cold injection.

17.2 Duration and Necessary Monitoring in Women Undergoing Therapy with Gonal-f® RFF Redi-ject®

Prior to beginning therapy with Gonal-f® RFF Redi-ject®, inform women about the time commitment and monitoring procedures necessary for treatment *[see Dosage and Administration (2.2, 2.3) and Warnings and Precautions (5.11)].*

17.3 Instructions Regarding a Missed Dose

Inform the woman that if she misses or forgets to take a dose of Gonal-f® RFF Redi-ject®, the next dose should not be doubled and she should call her healthcare provider for further dosing instructions.

17.4 Ovarian Hyperstimulation Syndrome

Inform women regarding the risks of OHSS *[see Warnings and Precautions (5.3)]* and OHSS-associated symptoms including lung and blood vessel problems *[see Warnings and Precautions (5.4)]* and ovarian torsion *[see Warnings and Precautions (5.5)]* with the use of Gonal-f® RFF Redi-ject®.

17.5 Multi-fetal Gestation and Birth

Inform women regarding the risk of multi-fetal gestation and birth with the use of Gonal-f® RFF Redi-ject® *[see Warnings and Precautions (5.6)]*

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