N19Z0103C

GONAL-f™ RFF Pen

(follitropin alfa injection)

*revised formulation female

PATIENT'S INFORMATION LEAFLET

Read the patient information before you start using the Gonal-f® RFF Pen. Read the patient information each time you get a refill, because there may be new information. This leaflet does not take the place of talking with your healthcare provider about your condition or treatment.

WHAT IS THE GONAL-f® RFF PEN?

The Gonal-f® RFF Pen is a prescription injectable medicine provided in a device that contains the hormone follicle stimulating hormone (FSH). FSH helps healthy ovaries to make eggs in women.

WHAT ARE THE USES OF THE GONAL-f® RFF PEN?

Doctors specializing in infertility or reproductive health prescribe the Gonal-f® RFF Pen to those patients needing medical assistance to have a child. After a thorough medical exam to determine your specific medical condition, your doctor may prescribe the Gonal-f® RFF Pen because you need help with producing eggs or you need supplementation as part of your treatment program. The Gonal-f® RFF Pen is used only for women seeking pregnancy. The Gonal-f® RFF Pen may be one of several drugs prescribed to you as part of your treatment program.

Gonal-f® RFF Pen is used:

- in certain infertile women to help with ovulation (production and release of a mature egg) and pregnancy. Gonal-f® RFF Pen will not help women whose ovaries no longer work because of a condition called primary ovarian failure.
- in women who are in an Assisted Reproductive Technology (ART) program, such as *in vitro* fertilization, to help their ovaries make more eggs.

WHO SHOULD NOT USE GONAL-f® RFF PEN?

Do not use the Gonal-f® RFF Pen if you:

- are allergic to recombinant human FSH products (see the end of this leaflet for a list of all the ingredients in the Gonal-f® RFF Pen)
- have primary ovarian failure (your ovaries no longer make eggs)
- are pregnant or think you may be pregnant
- have uncontrolled thyroid or adrenal problems
- have cancer in your female organs (ovaries, breast, uterus)
- have a pituitary tumor or other tumor in your brain
- have abnormal bleeding from your uterus or vagina
- have ovarian cysts or enlarged ovaries, not due to polycystic ovary syndrome (PCOS)

TELL YOUR HEALTHCARE PROVIDER IF YOU ARE BREASTFEEDING

It is not known if Gonal-f® RFF Pen passes into your milk.

CAN YOU USE THE GONAL-f® RFF PEN WITH OTHER MEDICINES?

Inform your doctor and pharmacist if you are taking or have taken any other medicines, including prescription and non-prescription medicines, vitamins, and herbal supplements. It is not known if Gonal-f® RFF Pen and other medicines can affect each other.

STORING THE GONAL-f® RFF PEN BEFORE THE FIRST USE

Store the Gonal-f® RFF Pen refrigerated (36°-46°F/2°-8°C) until dispensed. Upon dispensing, the Pen may be stored by the patient refrigerated (36°-46°F/2°-8°C) until the expiration date, or at room temperature (68°-77°F/20°-25°C) for up to three months or until the expiration date, whichever occurs first. Protect from light. Do not freeze.

HOW SHOULD I USE GONAL-f® RFF PEN?

- Use Gonal-f® RFF Pen exactly as prescribed. Your doctor will prescribe the dose that is right for you and your condition. Do not change the dose of Gonal-f® RFF Pen unless your doctor tells you to. Your doctor or healthcare provider will tell you the number of units (IU FSH) of Gonal-f® RFF Pen to use each day and the number of days to use the same Pen.
- Gonal-f® RFF Pen is given by an injection just under the skin (subcutaneous injection). Your doctor's office will teach you how to inject yourself. See the end of this leaflet for detailed instructions, "How do I prepare and use the Gonal-f® RFF Pen?" Do not inject Gonal-f® RFF Pen at home until your healthcare provider has taught you the correct way.
- Your condition must be closely monitored by your healthcare provider while you are using Gonal-f® RFF Pen. Your doctor may do regular ultrasound tests and blood tests to make sure that Gonal-f® RFF Pen is not making your ovaries too active (hyperstimulation) which can lead to rare, but serious side effects. Your doctor will decide if it is safe for you to continue with your fertility treatments based on the results of these tests.
- If you use too much Gonal-f® RFF Pen, call your doctor right away.
- Do not use Gonal-f® RFF Pen for a condition for which it was not prescribed. Do not give Gonal-f® RFF Pen to other people, even if they have the same symptoms you have.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF THE GONAL-f® RFF PEN?

The most common side effects with the Gonal-f® RFF Pen are headache, stomach pain, stomach bloating, nausea, and ovarian hyperstimulation syndrome. Bruising, pain, and redness can happen at the injection site.

Gonal-f® RFF Pen and other FSH products can cause serious side effects including:

- **Ovarian Hyperstimulation Syndrome (OHSS).** OHSS causes fluid to suddenly build up in the stomach area, chest area, and heart area. Stop using Gonal-f® RFF Pen and call your doctor right away if you get severe lower stomach area (pelvic) pain, nausea, vomiting, or weight gain.
- **Lung and blood vessel problems.** FSH products may cause serious lung problems including fluid in the lungs, trouble breathing, and worsening of asthma. Blood vessel problems include blood clots and strokes.
- **Multiple births.** FSH products can cause multiple births. Your healthcare provider will discuss your chances of multiple births.

These are not all the side effects of Gonal-f® RFF Pen. As with any medication, report any and all side effects, symptoms, or physical changes to your healthcare provider.

WHAT SHOULD YOU DO IF YOU FORGET TO TAKE YOUR DOSE?

Do NOT double the dose of Gonal-f® RFF Pen prescribed. Contact your doctor if you forget to take a dose of Gonal-f® RFF Pen.

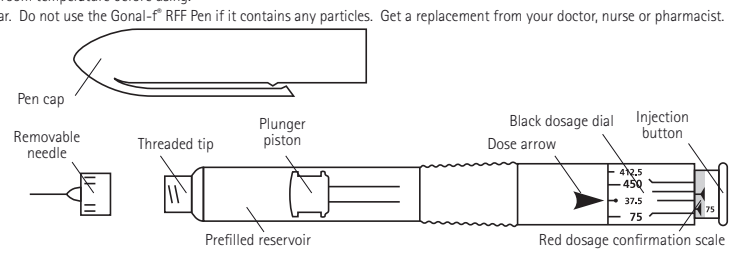
REVIEW THESE STEPS BEFORE YOU PREPARE OR ADMINISTER GONAL-f® RFF PEN

How do I prepare and use the Gonal-f® RFF Pen?

Getting ready

Make sure you have all the supplies listed below before you begin.

1. Gonal-f® RFF Pen
   - Make sure the Gonal-f® RFF Pen is at room temperature before using.
   - Make sure the liquid in the Pen is clear. Do not use the Gonal-f® RFF Pen if it contains any particles. Get a replacement from your doctor, nurse or pharmacist.



2. One new single-use, disposable administration needle supplied with the Gonal-f® RFF Pen.
3. Alcohol wipes and gauze pad.
4. Safety container (hard plastic or metal container) to use for safe disposal of used needles.

Before you start, wash your hands with soap and water. On a clean surface, lay out everything you need.

GONAL-f™ RFF Pen

(follitropin alfa injection)

*revised formulation female

For subcutaneous injection

DESCRIPTION

Gonal-f® RFF Pen (follitropin alfa injection) is a human follicle stimulating hormone (FSH) preparation of recombinant DNA origin, which consists 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 structures 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 Pen 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 Pen is a disposable, prefilled drug delivery system intended for the subcutaneous injection of multiple and variable doses of a liquid formulation of follitropin alfa.

Each Gonal-f® RFF Pen is filled with 415 IU (30 mcg), 568 IU (41 mcg), or 1026 IU (75 mcg) follitropin alfa to deliver at least 300 IU (22 mcg) in 0.5 mL, 450 IU (33 mcg) in 0.75 mL, or 900 IU (66 mcg) in 1.5 mL, respectively. Each Pen also contains 60 mg/mL sucrose, 3.0 mg/mL m-cresol, 1.1 mg/mL di-sodium hydrogen phosphate dihydrate, 0.45 mg/mL sodium dihydrogen phosphate monohydrate, 0.1 mg/mL methionine, 0.1 mg/mL Poloxamer 188. O-phosphoric acid and/or sodium hydroxide may be used for pH adjustment.

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

Therapeutic Class: Infertility

CLINICAL PHARMACOLOGY

Gonal-f® RFF Pen (follitropin alfa injection) stimulates ovarian follicular growth in women who do not have primary ovarian failure. FSH, the active component of Gonal-f® RFF Pen is the primary hormone responsible for follicular recruitment and development. In order to effect 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 Pen when monitoring of the patient indicates that sufficient follicular development has occurred. There is interpatient variability in response to FSH administration.

Pharmacokinetics

Single-dose pharmacokinetics of follitropin alfa were determined following subcutaneous administration of 300 IU Gonal-f® RFF Pen 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 1.

Table 1: Pharmacokinetic parameters of FSH following administration of Gonal-f® RFF Pen

Population Dose (IU)	Healthy Volunteers (n=21) 300 IU SC in a single dose	
	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 Pen following subcutaneous administration is slower than the elimination rate. Hence, the pharmacokinetics of Gonal-f® RFF Pen are absorption rate-limited.

Distribution

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

Metabolism/Excretion

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

Special populations: Safety, efficacy, and pharmacokinetics of Gonal-f® RFF Pen in patients with renal or hepatic insufficiency have not been established.

Drug–Drug Interactions: No drug-drug interaction studies have been conducted (see PRECAUTIONS).

CLINICAL STUDIES:

The safety and efficacy of Gonal-f® RFF have been examined in two clinical studies: one study (Study 22240) for ovulation induction and one study (Study 21884) for Assisted Reproductive Technologies (ART).

1. Ovulation Induction (OI):

Study 22240 was a phase III, assessor-blind, randomized, comparative, multinational, multicenter study in oligo-anovulatory infertile women undergoing ovulation induction. Patients 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. Efficacy was assessed using the mean ovulation rate in the first cycle of treatment. The cycle 1 ovulation rate (primary outcome) for Gonal-f® RFF is presented in Table 2. Additionally, this table includes cumulative secondary outcome results from cycle 1 through 3. Study 22240 was not powered to demonstrate differences in these secondary outcomes.

Table 2: Cumulative Ovulation and Clinical Pregnancy Rates in Ovulation Induction

Study 22240	**n=83**
Cumulative[a] Ovulation Rate	
Cycle 1	72%[b]
Cycle 2	89%[d]
Cycle 3	92%[d]
Cumulative[a] Clinical Pregnancy[c] Rate	
Cycle 1	28%[d]
Cycle 2	41%[d]
Cycle 3	45%[d]

a Cumulative rates were determined per patient 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 A clinical pregnancy was defined as a pregnancy during which a fetal sac (with or without heart activity) was visualized by ultrasound on day 34-36 after hCG administration.
d Secondary efficacy parameter. Study 22240 was not powered to demonstrate differences in this parameter.

2. Assisted Reproductive Technologies (ART):

Study 21884 was a phase III, assessor-blind, randomized, comparative, multinational, multicenter study in ovulatory, infertile women undergoing stimulation of multiple follicles for Assisted Reproductive Technologies (ART) after pituitary down-regulation with a GnRH agonist. Patients were randomized to either Gonal-f® RFF (n=237), administered subcutaneously, or a comparator recombinant human FSH. Randomization was stratified by insemination technique [conventional *in-vitro* fertilization (IVF) vs. intra-cytoplasmic sperm injection (ICSI)]. Efficacy was assessed using the mean number of fertilized oocytes the day after insemination. The initial doses of Gonal-f® RFF were 150 IU a day for patients < 35 years old and 225 IU for patients ≥ 35 years old. The maximal dose allowed for both age groups was 450 IU per day. Treatment outcomes for Gonal-f® RFF are summarized in Table 3.

Table 3: Treatment Outcomes in ART

Study 21884	**value (n)**
Mean number of 2PN oocytes per patient	6.3 (237)[a]
Mean number of 2PN oocytes per patient receiving IVF	6.1 (88)[b]
Mean number of 2PN oocytes per patient 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 Study 21884 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 parameter. Study 21884 was not powered to demonstrate differences in this parameter.

INDICATIONS AND USAGE

Gonal-f® RFF Pen (follitropin alfa injection) is indicated for the induction of ovulation and pregnancy in the oligo-anovulatory infertile patient in whom the cause of infertility is functional and not due to primary ovarian failure. Gonal-f® RFF Pen is also indicated for the development of multiple follicles in the ovulatory patient participating in an Assisted Reproductive Technology (ART) program.

Selection of Patients:

1. Before treatment with Gonal-f® RFF Pen is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. This should include an assessment of pelvic anatomy. Patients with tubal obstruction should receive Gonal-f® RFF Pen only if enrolled in an *in vitro* fertilization program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Appropriate evaluation should be performed to exclude pregnancy.
4. Patients in later reproductive life have a greater predisposition to endometrial carcinoma as well as a higher incidence of anovulatory disorders. A thorough diagnostic evaluation should always be performed in patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities before starting Gonal-f® RFF Pen therapy.
5. Evaluation of the partner's fertility potential should be included in the initial evaluation.

CONTRAINDICATIONS

Gonal-f® RFF Pen (follitropin alfa injection) is contraindicated in women who exhibit:

1. Prior hypersensitivity to recombinant FSH preparations or one of their excipients.
2. High levels of FSH indicating primary gonadal failure.
3. Uncontrolled thyroid or adrenal dysfunction.
4. Sex hormone dependent tumors of the reproductive tract and accessory organs.
5. An organic intracranial lesion such as a pituitary tumor.
6. Abnormal uterine bleeding of undetermined origin (see "Selection of Patients").
7. Ovarian cyst or enlargement of undetermined origin, not due to polycystic ovary syndrome (see "Selection of Patients").
8. Pregnancy.

WARNINGS

Gonal-f® RFF Pen (follitropin alfa injection) should only be used by physicians who are thoroughly familiar with infertility problems and their management.

Gonal-f® RFF Pen is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome (OHSS) in women with or without pulmonary or vascular complications. Gonadotropin therapy requires a certain time commitment by physicians and supportive health professionals, and requires the availability of appropriate monitoring facilities (see "Precautions/Laboratory Tests"). Safe and effective use of Gonal-f® RFF Pen in women requires monitoring of ovarian response with serum estradiol and vaginal ultrasound on a regular basis. The lowest effective dose should be used.

Overstimulation of the Ovary During FSH Therapy:

Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distention and/or abdominal pain occurs in approximately 20% of those treated with urofollitropin and hCG, and generally regresses without treatment within two or three weeks. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Gonal-f® RFF Pen therapy, hCG should not be administered in this course of therapy. This will reduce the chances of development of Ovarian Hyperstimulation Syndrome.

Ovarian Hyperstimulation Syndrome (OHSS): OHSS is a medical event distinct from uncomplicated ovarian enlargement. Severe OHSS may progress rapidly (within 24 hours to several days) to become a serious medical event. It is characterized by an apparent 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. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see "Pulmonary and Vascular Complications"). Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with Ovarian Hyperstimulation Syndrome (OHSS).

OHSS occurred in 6 of 83 (7.2%) Gonal-f® RFF treated women in Study 22240 (ovulation induction); none were classified as severe. In Study 21884 (ART), OHSS occurred in 11 of 237 (4.6%) Gonal-f® RFF treated women and 1 (0.42%) was classified as severe. OHSS may be more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore, patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about seven to ten days following treatment. Usually, OHSS resolves spontaneously with the onset of menses. If there is evidence that OHSS may be developing prior to hCG administration (see "Precautions / Laboratory Tests"), the hCG must be withheld.

If severe OHSS occurs, treatment must be stopped and the patient should be hospitalized.

A physician experienced in the management of this syndrome, or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

Pulmonary and Vascular Complications:

Serious pulmonary conditions (e.g., atelectasis, acute respiratory distress syndrome and exacerbation of asthma) have been reported. In addition, thromboembolic events both in association with, and separate from Ovarian Hyperstimulation Syndrome have been reported. Intravascular thrombosis and embolism can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple Births: Reports of multiple births have been associated with Gonal-f® RFF treatment. In Study 22240 for women receiving Gonal-f® RFF over three treatment cycles, 20% of live births were multiple births. In Study 21884, 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. The patient should be advised of the potential risk of multiple births before starting treatment.

PRECAUTIONS

General: Careful attention should be given to the diagnosis of infertility in candidates for Gonal-f® RFF Pen (follitropin alfa injection) therapy (see "Indications and Usage/ Selection of Patients").

Information for Patients: Prior to therapy with Gonal-f® RFF Pen, patients should be informed of the duration of treatment and monitoring of their condition that will be required. The risks of Ovarian Hyperstimulation Syndrome and multiple births in women (see **WARNINGS**) and other possible adverse reactions (see **"Adverse Reactions"**) should also be discussed.

A 'Patient's Information Leaflet' is provided for patients prescribed Gonal-f® RFF Pen.

Laboratory Tests: In most instances, treatment of women with Gonal-f® RFF Pen results only in follicular recruitment and development. In the absence of an endogenous LH surge, hCG is given 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 levels. The combination of both ultrasound and serum estradiol measurement are useful for monitoring the development of follicles, for timing of the ovulatory trigger, as well as for detecting ovarian enlargement and minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestation. It is recommended that the number of growing follicles be confirmed using ultrasonography because plasma estrogens do not give an indication of the size or number of follicles.

The clinical confirmation of ovulation, with the exception of pregnancy, is obtained by direct and indirect indices of progesterone production. The indices most generally used are as follows:

1. A rise in basal body temperature;
2. Increase in serum progesterone; and
3. Menstruation following a shift in basal body temperature.

When used in conjunction with the indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:

1. Fluid in the cul-de-sac;
2. Ovarian stigmata;
3. Collapsed follicle; and
4. Secretory endometrium.

Accurate interpretation of the indices of follicle development and maturation require a physician who is experienced in the interpretation of these tests.

Drug Interactions: No drug/drug interaction studies have been performed.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Gonal-f® RFF Pen. 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 (≥40 IU/kg/day) for extended periods, through reduced fecundity.

Pregnancy: Pregnancy Category X. See CONTRAINDICATIONS.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant from Gonal-f® RFF Pen, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

The safety of Gonal-f® RFF was examined in two clinical studies [(one ovulation induction study (n=83) and one study in ART (n=237)].

Adverse events (without regard to causality assessment) occurring in at least 2.0% of patients in Study 22240 (ovulation induction) are listed in Table 4.

Table 4: Safety Profile in Ovulation Induction Study 22240

Body System Preferred Term	**Patients (%) Experiencing Events** **Treatment cycles = 176*** **n=83†**
Central and Peripheral Nervous System	
Headache	22 (26.5%)
Dizziness	2 (2.4%)
Migraine	3 (3.6%)
Gastro-intestinal System	
Abdominal Pain	10 (12.0%)
Nausea	3 (3.6%)
Flatulence	3 (3.6%)
Diarrhea	3 (3.6%)
Toothache	3 (3.6%)
Dyspepsia	2 (2.4%)
Constipation	2 (2.4%)
Stomatitis Ulcerative	2 (2.4%)
Neoplasm	
Ovarian Cyst	3 (3.6%)
Reproductive, Female	
Ovarian Hyperstimulation	6 (7.2%)
Breast Pain Female	5 (6.0%)
Vaginal Haemorrhage	5 (6.0%)
Gynecological-related pain	2 (2.4%)
Uterine haemorrhage	2 (2.4%)
Respiratory System	
Sinusitis	5 (6.0%)
Pharyngitis	6 (7.2%)
Rhinitis	6 (7.2%)
Coughing	2 (2.4%)
Application Site	
Injection Site Pain	4 (4.8%)
Injection Site Inflammation	2 (2.4%)
Body as a Whole- General	
Back Pain	3 (3.6%)
Pain	2 (2.4%)
Fever	2 (2.4%)
Hot Flushes	2 (2.4%)
Malaise	2 (2.4%)
Skin and Appendages	
Acne	3 (3.6%)
Urinary System	
Micturition Frequency	2 (2.4%)
Cystitis	2 (2.4%)
Resistance Mechanism	
Infection viral	2 (2.4%)

* up to 3 cycles of therapy
† total patients treated with Gonal-f® RFF

Item code	Item Description	Replaces item code	Folded Size	Remarks
N19Z0103C	FPP GONAL-F RFF NG PEN AD USA C	N19Z0103B	160 x 36 mm	The yellow broken line shall not be printed, but it indicate the perforation

280x480 mm - ist-1600 - Black

Preparing the Pen

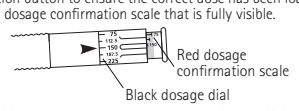
Note: Read steps 1 through 7 prior to pulling the injection button on the pen. Do not pull the injection button until the dose is dialed and you are ready for injection.

1. Remove the protective pen cap. Clean threaded tip of pen with an alcohol swab.
2. Take a single-use disposable needle provided in the Gonal-f® RFF Pen carton. If the peel tab of the needle is damaged or loose, do not use it. Discard the needle and take a new one. Remove the peel tab from the outer needle cap.
3. With the tab removed, hold the outer needle cap firmly in one hand and hold the pen firmly in the other hand. Press the threaded tip of the Gonal-f® RFF Pen into the open end of the needle cap and twist it clockwise until it is securely fixed.
4. Once the needle is securely attached, remove the outer needle cap by gently pulling it straight off. Do NOT remove the inner needle cap—leave it where it is. Do NOT throw away the outer needle cap—you will need it when you are ready to remove the needle following your injection.

Note: Use only the single-use disposable needles provided within the Gonal-f® RFF Pen carton or compatible needles distributed separately by EMD Serono, Inc.

This step only needs to be performed before the first use of each new pen; Otherwise, proceed to Step 6.

5. You must prime the Pen before the first use. You only need to prime the first time you use a new pen. Do the following steps to get your pen ready for use:
   - Check to make sure the dose arrow is set at 37.5. If not, turn the dosage dial (black numbers) to align the dose arrow with 37.5.
   - Pull out the injection button as far as it will go.
   - Remove the inner needle cap and hold the Pen with the needle pointing upwards.
   - Tap the drug reservoir gently with your finger so that any air bubbles rise up towards the needle. (If a few small air bubbles remain, do not worry; this is normal).
   - Keep the needle pointing upright and push in the injection button completely. Stop pushing after you hear the first click. A small amount of liquid should come out of the needle indicating that the pen is ready for use. The amount of liquid seen at the needle tip is part of the extra medicine from the Pen. If no liquid appears the first time, repeat these steps until liquid comes out of the needle tip.
   - Replace the inner needle cap.
6. Select your prescribed dose by turning the dosage dial (black numbers) to the proper dose mark on the dial in front of the arrow mark. Carefully check the dosage dial before proceeding. Once you have set the dose correctly, load the Pen by pulling out the injection button straight as far as it will go. Do not twist the injection button while loading the pen.
7. Check the red dosage confirmation scale on the injection button to ensure the correct dose has been loaded and that the accurate dose will be injected. The loaded dose is shown by the last mark (flat arrow) on the red dosage confirmation scale that is fully visible.

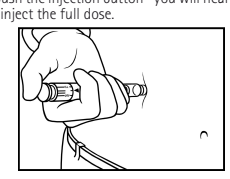


- If you accidentally pull out the injection button with an incorrect dose setting, do not inject. If the set dose is lower than the correct dose to be administered, you can turn the dosage dial to the correct dose and pull out the injection button again. If the set dose is higher than the dose to be administered, discard the dose by pushing all the liquid out into the safety container and repeat the previous steps for setting the dose.

Injecting the dose

Suitable injection sites on the stomach will be advised by your fertility specialist. Occasionally, your fertility specialist may suggest an alternative site.

8. Clean the injection site with an alcohol swab and allow it to air dry.
9. Remove the inner needle cap from the needle on the Pen. Do not touch the needle or allow the needle to touch any surface.
10. To inject, insert the needle into the skin at a 90° angle and push the injection button—you will hear the button clicking. After the last click, allow the needle to remain in the skin for at least 5 seconds. This will ensure that you inject the full dose.



11. After the injection is complete, keep the injection button pressed down and remove the needle out of your skin. Apply pressure using a gauze pad.
12. Each time you finish an injection, remove and discard the used needle as follows. Hold the Gonal-f® RFF Pen firmly by the drug reservoir. Carefully replace the outer needle cap onto the needle. Gripping the outer needle cap firmly, remove the needle by unscrewing the Pen counter-clockwise and dispose of the needle in your safety container.
13. Replace the Pen cap and store properly. See the section "Storing the Gonal-f® RFF Pen Between Uses."

If there is not enough medicine remaining in the Gonal-f® RFF Pen.

- After several doses, you may not have enough Gonal-f® RFF remaining in the Pen to administer another full dose. The red dosage confirmation scale on the injection button enables you to check that the correct dose has been loaded. Dial your dose and pull out the injection button. It will go out only as far as the amount of drug that is left in the Pen. The amount of drug left in the Pen will be indicated by the last mark (flat arrow) on the red dosage confirmation scale that is fully visible. If this amount is lower than the set dose, the amount of Gonal-f® RFF left in the Pen is not enough to complete your full dose. If the loaded dose is not sufficient to complete your injection you have two options:
- Inject the partial dose (what is left in the Pen) and then immediately complete the dose with a new Gonal-f® RFF Pen, remembering to measure out only what is required to complete your daily dose.
- Discard the Gonal-f® RFF Pen and inject the full dose using a new Pen.

It is common for a small amount of drug to be leftover in the Gonal-f® RFF Pen. This is normal. Any drug remaining in the Gonal-f® RFF Pen after your treatment is complete should be discarded.

Storing the Gonal-f® RFF Pen Between Uses

- After each use, the Gonal-f® RFF Pen must be stored away from light and may be stored refrigerated or at room temperature between 36°– 77° F (2°- 25° C) for up to 28 days.
- Do not store above 77°F (25°C).
- If you are traveling, keep the Gonal-f® RFF Pen stored away from light and extreme temperatures. Do not freeze.
- Allow the liquid solution to adjust to room temperature prior to administering your injection.
- Check that the liquid is clear. Do not use if it contains any particles. Report this to your doctor, nurse or pharmacist immediately.
- Keep the Gonal-f® RFF Pen and all medicines out of the reach of children.

What are the ingredients in Gonal-f® RFF Pen?

Active ingredient: follitropin alfa (r-hFSH)

Inactive ingredients: sucrose, meta-cresol, di-sodium hydrogen phosphate dihydrate, sodium dihydrogen phosphate monohydrate, methionine, Poloxamer 188, O-phosphoric acid and/or sodium hydroxide

Where can more information about the Gonal-f® RFF Pen be obtained?

This leaflet is a summary of the important patient information about the Gonal-f® RFF Pen. If you have any questions or problems, talk to your doctor or other health care provider. The Gonal-f® RFF Pen is manufactured and distributed by EMD Serono, Inc. You can also call toll free 1 866-LETS TRY (1-866-538-7879) or log on to www.fertilitylifelines.com.

Revised October 2008

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Headache occurred in greater than 20% of patients receiving Gonal-f® RFF in this study.

Adverse events (without regard to causality assessment) occurring in at least 2.0% of patients in Study 21884 (ART) are listed in Table 5.

Table 5: Safety Profile in Assisted Reproductive Technologies Study 21884

Body System Preferred Term	**Patients (%) Experiencing Events n=237†**
Gastro-intestinal System	
Abdominal Pain	55 (23.2%)
Nausea	19 (8.0%)
Body as a Whole– General	
Abdomen Enlarged	33 (13.9%)
Pain	7 (3.0%)
Central and Peripheral Nervous System	
Headache	44 (18.6%)
Dizziness	5 (2.1%)
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%)
Intermenstrual Bleeding	9 (3.8%)

† total patients treated with Gonal-f® RFF

Headache and abdomen enlargement occurred in more than 10% of patients and abdominal pain occurred in more than 20% of patients.

The following medical events have been reported subsequent to pregnancies resulting from gonadotropins therapy in controlled clinical studies:

1. Spontaneous Abortion
2. Ectopic Pregnancy
3. Premature Labor
4. Postpartum Fever
5. Congenital Abnormalities

There are no indications that use of gonadotropins during ART is associated with an increased risk of congenital malformations.

The following adverse reactions have been previously reported during Gonal-f® RFF therapy:

1. Pulmonary and vascular complications (see "WARNINGS"),
2. Adnexal torsion (as a complication of ovarian enlargement),
3. Mild to moderate ovarian enlargement,
4. Hemoperitoneum

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

Post Marketing Reports

During post-market surveillance, reports of hypersensitivity reactions including anaphylactoid reactions have been reported with the use of Gonal-f® RFF.

OVERDOSAGE

Aside from possible ovarian hyperstimulation and multiple gestations (see "WARNINGS"), there is no information on the consequences of acute overdosage with Gonal-f® RFF Pen (follitropin alfa injection).

DOSAGE AND ADMINISTRATION

The Gonal-f® RFF Pen delivery system delivers at least 300 IU, 450 IU, or 900 IU, equivalent to a maximum of four 75 IU injections, six 75 IU injections or twelve 75 IU injections, respectively. The minimum dose that can be set is 37.5 IU; the maximum dose that can be set is 300 IU (for 300 IU delivery system) or 450 IU (for 450 IU and 900 IU delivery system).

Dosage:

Infertile Patients with Oligo-Anovulation: The dose of Gonal-f® RFF Pen (follitropin alfa injection) to stimulate development of the follicle must be individualized for each patient.

The lowest dose consistent with the expectation of good results should be used. Over the course of treatment, doses of Gonal-f® RFF Pen may range up to 300 IU per day depending on the individual patient response. Gonal-f® RFF Pen should be administered until adequate follicular development is indicated by serum estradiol and vaginal ultrasonography. A response is generally evident after 5 to 7 days. Subsequent monitoring intervals should be based on individual patient response.

It is recommended that the initial dose of the first cycle be 75 IU of Gonal-f® RFF Pen per day, administered subcutaneously. An incremental adjustment in dose of up to 37.5 IU may be considered after 14 days. Further dose increases of the same magnitude could be made, if necessary, every seven days. Treatment duration should not exceed 35 days unless an E2 rise indicates imminent follicular development. To complete follicular development and effect ovulation in the absence of an endogenous LH surge, chorionic gonadotropin, hCG, should be given after the last dose of Gonal-f® RFF Pen. Chorionic gonadotropin should be withheld if the serum estradiol is greater than 2,000 pg/mL. If the ovaries are abnormally enlarged or abdominal pain occurs, Gonal-f® RFF Pen treatment should be discontinued, hCG should not be administered, and the patient should be advised not to have intercourse; this may reduce the chance of development of the Ovarian Hyperstimulation Syndrome and, should spontaneous ovulation occur, reduce the chance of multiple gestation. A follow-up visit should be conducted in the luteal phase.

The initial dose administered in the subsequent cycles should be individualized for each patient based on her response in the preceding cycle. Doses larger than 300 IU of FSH per day are not routinely recommended. As in the initial cycle, hCG must be given after the last dose of Gonal-f® RFF Pen to complete follicular development and induce ovulation. The precautions described above should be followed to minimize the chance of development of the Ovarian Hyperstimulation Syndrome.

The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational activity. Care should be taken to ensure insemination. In light of the indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Gonal-f® RFF Pen.

Assisted Reproductive Technologies: As in the treatment of patients with oligo-anovulatory infertility, the dose of Gonal-f® RFF Pen to stimulate development of the follicle must be individualized for each patient. For Assisted Reproductive Technologies, therapy with Gonal-f® RFF Pen should be initiated in the early follicular phase (cycle day 2 or 3) at a dose of 150 IU per day administered subcutaneously, until sufficient follicular development is attained. In most cases, therapy should not exceed ten days.

In patients undergoing ART under 35 years old, whose endogenous gonadotropin levels are suppressed, Gonal-f® RFF Pen should be initiated at a dose of 150 IU per day. In patients 35 years old and older whose endogenous gonadotropin levels are suppressed, Gonal-f® RFF Pen should be initiated at a dose of 225 IU per day. Treatment should be continued until adequate follicular development is indicated as determined by ultrasound in combination with measurement of serum estradiol levels. Adjustments to dose may be considered after five days based on the patient's response; subsequently dosage should be adjusted no more frequently than every 3-5 days and by no more than 75-150 IU additionally at each adjustment. Doses greater than 450 IU per day are not recommended. Once adequate follicular development is evident, hCG should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing OHSS.

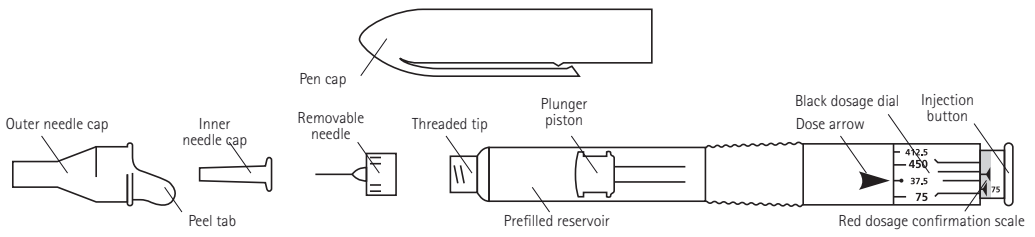
Administration:

Administer subcutaneously in the abdomen as described in the 'Patient's Information Leaflet' provided for patients prescribed Gonal-f® RFF Pen.

Patient Instructions for Use

Make sure you have all the supplies listed below before you begin.

1. Gonal-f® RFF Pen
   - Make sure the Gonal-f® RFF Pen is at room temperature before using.
   - Make sure the liquid in the Pen is clear. Do not use the Gonal-f® RFF Pen if it contains any particles. Get a replacement from your doctor, nurse or pharmacist.



2. One new single-use, disposable administration needle supplied with the Gonal-f® RFF Pen.
3. Alcohol wipes and gauze pad.
4. Safety container (hard plastic or metal container) to use for safe disposal of used needles.

Before you start, wash your hands with soap and water. On a clean surface, lay out everything you need.

Preparing the Pen

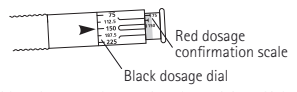
Note: Read steps 1 through 7 prior to pulling the injection button on the pen. Do not pull the injection button until the dose is dialed and you are ready for injection.

1. Remove the protective pen cap. Clean threaded tip of pen with an alcohol swab.
2. Take a single-use disposable needle provided in the Gonal-f® RFF Pen carton. If the peel tab of the needle is damaged or loose, do not use it. Discard the needle and take a new one. Remove the peel tab from the outer needle cap.
3. With the tab removed, hold the outer needle cap firmly in one hand and hold the Pen firmly in the other hand. Press the threaded tip of the Gonal-f® RFF Pen into the open end of the needle cap and twist it clockwise until it is securely fixed.
4. Once the needle is securely attached, remove the outer needle cap by gently pulling it straight off. Do NOT remove the inner needle cap—leave it where it is. Do NOT throw away the outer needle cap—you will need it when you are ready to remove the needle following your injection.

Note: Use only the single-use disposable needles provided within the Gonal-f® RFF Pen carton or compatible needles distributed separately by EMD Serono, Inc.

Step 5 only needs to be performed before the first use of each new Pen; Otherwise, proceed to Step 6.

5. You must prime the Pen before the first use. You only need to prime the first time you use a new Pen. Do the following steps to get your Pen ready for use:
   - Check to make sure the dose arrow is set at 37.5. If not, turn the dosage dial (black numbers) to align the dose arrow with 37.5.
   - Pull out the injection button as far as it will go.
   - Remove the inner needle cap and hold the Pen with the needle pointing upwards.
   - Tap the drug reservoir gently with your finger so that any air bubbles rise up towards the needle. (If a few small air bubbles remain, do not worry; this is normal).
   - Keep the needle pointing upright and push in the injection button completely. Stop pushing after you hear the first click. A small amount of liquid should come out of the needle indicating that the pen is ready for use. The amount of liquid seen at the needle tip is part of the extra medicine from the Pen. If no liquid appears the first time, repeat these steps until liquid comes out of the needle tip.
   - Replace the inner needle cap.
6. Select your prescribed dose by turning the dosage dial (black numbers) to the proper dose mark on the dial in front of the arrow mark. Carefully check the dosage dial before proceeding. Once you have set the dose correctly, load the Pen by pulling out the injection button straight as far as it will go. Do not twist the injection button while loading the pen.
7. Check the red dosage confirmation scale on the injection button to ensure the correct dose has been loaded and that the accurate dose will be injected. The loaded dose is shown by the last mark (flat arrow) on the red dosage confirmation scale that is fully visible.

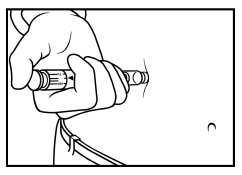


- If you accidentally pull out the injection button with an incorrect dose setting, do not inject. If the set dose is lower than the correct dose to be administered, you can turn the dosage dial to the correct dose and pull out the injection button again. If the set dose is higher than the dose to be administered, discard the dose by pushing all the liquid out into the safety container and repeat the previous steps for setting the dose.

Injecting the dose

Suitable injection sites on the stomach will be advised by your fertility specialist. Occasionally, your fertility specialist may suggest an alternative site.

8. Clean the injection site with an alcohol swab and allow it to air dry.
9. Remove the inner needle cap from the needle on the Pen. Do not touch the needle or allow the needle to touch any surface.
10. To inject, insert the needle into the skin at a 90° angle and push the injection button—you will hear the button clicking. After the last click, allow the needle to remain in the skin for at least 5 seconds. This will ensure that you inject the full dose.



11. After the injection is complete, keep the injection button pressed down and remove the needle out of your skin. Apply pressure using a gauze pad.
12. Each time you finish an injection, remove and discard the used needle as follows. Hold the Gonal-f® RFF Pen firmly by the drug reservoir. Carefully replace the outer needle cap onto the needle. Gripping the outer needle cap firmly, remove the needle by unscrewing the Pen counter-clockwise and dispose of the needle in your safety container.
13. Replace the Pen cap and store properly. See "HOW SUPPLIED."

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

Gonal-f® RFF Pen (follitropin alfa injection) is a disposable, prefilled multiple-dose delivery system containing a sterile, ready-to-use liquid formulation of follitropin alfa. Each Gonal-f® RFF Pen is filled with 415 IU, 568 IU, or 1026 IU follitropin alfa to deliver a minimum total of 300 IU in 0.5 mL, 450 IU in 0.75 mL, or 900 IU in 1.5 mL, respectively. Each Pen is supplied in a carton containing 29G x 1/2 inch disposable needles to be used for administration.

The following package combinations are available:

NDC 44087-1113-1 One Gonal-f® RFF Pen contains 415 IU to deliver a minimum total of 300 IU/0.5 mL and 5 single-use disposable 29G x ½" needles

NDC 44087-1112-1 One Gonal-f® RFF Pen contains 568 IU to deliver a minimum total of 450 IU/0.75 mL and 7 single-use disposable 29G x ½" needles

NDC 44087-1114-1 One Gonal-f® RFF Pen contains 1026 IU to deliver a minimum total of 900 IU/1.5 mL and 14 single-use disposable 29G x ½" needles

Store the Gonal-f® RFF Pen refrigerated (2°-8°C/36°-46°F) until dispensed. Upon dispensing, the patient may store the pen refrigerated (2°-8°C/36°-46°F) until the expiration date, or at room temperature (20°-25°C/68°-77°F) for up to three months or until the expiration date, whichever occurs first. After the first injection, the pen may be stored refrigerated (2°-8°C/36°-46°F) or at room temperature (20°-25°C/68°-77°F) for up to 28 days. Protect from light. Do not freeze. Discard unused material after 28 days.

Rx only

Manufactured for: EMD Serono, Inc., Rockland, MA 02370 U.S.A.

Revised: October 2008

N19Z0103C

ist-1600

Item code	Item Description	Replaces item code	Folded Size	Remarks
N19Z0103C	FPP GONAL-F RFF NG PEN AD USA C	N19Z0103B	160 x 36 mm	The yellow broken line shall not be printed, but it indicate the perforation

280x480 mm - ist-1600 - Black